ATX-101 (DEOXYCHOLIC ACID) INJECTION

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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1. EXECUTIVE SUMMARY

Introduction

ATX-101 (deoxycholic acid [DCA] injection) is a first-in-class, injectable drug that has been developed for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF). Submental fat is of particular concern for many individuals. The presence of unwanted SMF, and associated fullness/convexity of the submental area, can affect youthful appearance and the judgments of attractiveness from others. Excess SMF, which can arise due to aging, lifestyle, or genetic predisposition, is often resistant to resolution (improvement) through diet and exercise (Schlessinger et al., 2013; Duncan and Chubaty, 2006; Patel, 2006; Rzany, 2014). Many of the patients who are seen by aesthetic medicine specialists (dermatologists, dermatological surgeons, plastic surgeons) report distress associated with excess SMF and a desire to have access to relatively noninvasive treatment (Schlessinger et al., 2013). Current treatment options are limited to traditional aesthetic surgical procedures performed under general anesthesia as well as targeted liposuction, which may be performed under general or local anesthesia (Schlessinger et al., 2013). ATX-101 is an important treatment option for aesthetically-minded patients who are interested in using injectable treatments and prefer not to have surgery.

The specific proposed indication is:

ATX-101 (deoxycholic acid injection) is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

ATX-101 is supplied as a sterile solution in single-use vials containing 2 mL of a 10 mg/mL (1% weight/volume) solution in phosphate-buffered saline (PBS) with 0.9% benzyl alcohol (BA) as a preservative. It is intended to be administered in 0.2-mL injections spaced 1-cm apart into the subcutaneous (SC) fat using a 30 gauge (or smaller) 0.5-inch needle. The dosing regimen results in an area-adjusted dose of 2 mg/cm^2 and the maximum intended dose in any individual treatment session is 100 mg (ie, 10 mL). Treatments are given at intervals of not less than 4 weeks until the desired result is achieved, to a maximum of 6 treatment sessions. The total dose of ATX-101 administered in each treatment session and the overall number of treatments are tailored to the individual patient based on the amount and distribution of SMF as well as the patient's desired result. Desired results are gradual and typically reached in fewer than 6 treatments (most patients experience improvement in 2 to 4 treatments). Clinical studies have demonstrated maintenance of effect for up to 4 years. Unlike other aesthetic injectables (botulinum toxins or dermal fillers), retreatment with ATX-101 is unlikely given that its mechanism of action involves the destruction of fat cells. Patients, in consultation with their physicians, will be able to weigh the benefits and risks of treatment with ATX-101 on an ongoing basis and decide whether or not to initiate and/or continue treatment.

Clinical Relevance and Unmet Need

Cervical rhytidectomy, or necklift, is a surgical procedure that removes localized fat deposits under the chin, corrects muscle laxity, and tightens/removes sagging skin in this region. The necklift procedure involves making incisions around the ears and sometimes under the chin to

access and remove the underlying unwanted fat and to tighten the platysma muscle. Healing may take weeks or months and may be significantly prolonged in certain individuals such as smokers and diabetics (Gryskiewicz, 2003). Potential complications include bleeding, infection, nerve injury, scarring, risks associated with general anesthesia, dyspigmentation, and death. Unsightly bruising and swelling may extend patient "down time" and restrict patient's activities (Bitar and Giampapa, 2008).

Liposuction, with or without platysmaplasty, is an option for patients with sufficient skin tone to enable subsequent skin contraction and adherence (Gryskiewicz, 2003). This procedure has typically been used in younger patients and as an adjunct to face and neck lifts in older patients. Complications of submental liposuction include contour irregularities (rippling and divots), adherence of skin to underlying muscle, exposure of platysmal bands, scarring, bruising, risks associated with anesthesia (if utilized), painful recovery periods, or death (Bitar and Giampapa, 2008). For many patients, these procedures may be unsuitable or contraindicated because of physical or other considerations, or they may not believe that the risk/benefit profile is acceptable due to the potential for scarring, bruising, and painful recovery periods, or surgical revision to achieve or maintain the desired outcome.

Nonsurgical treatment strategies for SMF reduction have been pursued in an attempt to address some of the potential shortcomings and invasive nature of the traditional surgical treatment options. A broad range of fat reducing injection procedures are offered under the very loosely characterized umbrella of procedures known as "mesotherapy." None of the current mesotherapy treatments for fat reduction have undergone formal drug registration processes, and neither efficacy nor safety has been established in appropriately controlled clinical studies. With respect to fat reduction, the ablative type of mesotherapy that leads to the destruction of fat cells, is usually performed with a mixture of phosphatidylcholine (PC) and deoxycholate (DC) or DC and other putative active ingredients.

Use of PC/DC became increasingly popular in the United States (US) starting in the mid-1990s, and some US physicians and aesthetic clinics utilized unapproved and unregulated formulations of PC/DC either by illegally importing Lipostabil® (a product approved in some countries in the European Union [EU], but not in the US), or by using compounding pharmacies to prepare PC/DC formulations from unspecified animal-derived sources (ie, lipodissolve, lipotherapy, mesotherapy, or injection lipolysis). On 07 April 2010, the Food and Drug Administration (FDA) issued Warning Letters to 6 US medical spas (cosmetic medical businesses that operate under the supervision of a licensed health care professional) indicating that they were making false and misleading claims about their PC/DC-containing products. The FDA clarified that PC/DC is an unapproved drug.

No drug product has been registered for the reduction of localized fat deposits in the US. The availability of an approved product will provide physicians and patients with a minimally-invasive, safe, and clinically-proven alternative to current treatment options. Moreover, a regulated product will be manufactured in accordance with good manufacturing practice (GMP) standards, closely monitored for ongoing safety signals, and provided with an FDA-approved package insert as well as physician training/education. Topics covered in the product labeling will include use of the correct number and locations for injections, proper administration techniques, and pain management options. Thus, ATX-101 represents an important, nonsurgical treatment for the increasing demand for SMF reduction and serves as a regulated alternative to

unregulated, compounded, and misbranded lipolytic products with unknown quality, safety, and efficacy.

Background and Mechanism of Action

Deoxycholic acid is a well-characterized endogenous secondary bile acid that serves to emulsify and solubilize dietary fat, thereby aiding in its breakdown and absorption within the gut. As exogenously administered DC from synthetic DCA and endogenous DC are biologically identical, the terms deoxycholic acid and deoxycholate may be used interchangeably. Deoxycholate has been safely used as a solubilizing excipient for many years in globally approved drug products, including the antifungal amphotericin B (Amphotericin B for Injection USP Prescribing Information; approximately 54 mg of DC per day for a 70 kg patient), and is also found in influenza vaccines in which it is utilized to disrupt the virus during manufacturing (Fluarix® and Flulaval® Prescribing Information).

In 2004, Rotunda and colleagues reported that DC, and not PC, was the pharmacologically active constituent in PC/DC mixtures responsible for the reduction of localized SC fat (Rotunda et al., 2004). Further in vitro and in vivo studies subsequently confirmed that, when injected into SC fat, DC physically disrupts the cell membrane of adipocytes causing adipocytolysis, and that PC actually inhibits the activity of DC (Rotunda et al., 2004; Rotunda et al., 2005; Thuangtong et al., 2010). In addition, the activity of DC is attenuated by protein, making its adipocytolytic effect more potent in protein-poor tissues such as SC fat as compared with nearby protein-rich tissues such as skin, muscle, and blood vessels (Thuangtong et al., 2010). Additional nonclinical studies indicate that the local adipocytolysis caused by DC elicits a predictable tissue response in which macrophages are attracted to the area to eliminate cellular debris and lipids, which are then cleared through natural processes (Cinti et al., 2005). This is followed by the appearance of fibroblasts and observed thickening of fibrous septa, suggesting an increase in total collagen (ie, neocollagenesis). This mechanism of action is supported by Kythera Biopharmaceuticals, Inc. (Kythera)'s nonclinical study results and by Phase 1 clinical histology findings (Section 2.2).

Nonclinical Development Program

Although DCA is a well-characterized endogenous substance, Kythera completed a comprehensive panel of nonclinical studies to characterize the toxicity and safety profile of ATX-101, including:

1) In vitro and in vivo pharmacology studies (nonclinical efficacy);
2) Cardiovascular, respiratory and central nervous system safety pharmacology studies;
3) Absorption, distribution and toxicokinetic studies;
4) Single-dose through chronic repeat-dose toxicity, reproductive and genetic toxicology studies;
5) Synthetic DCA and animal-derived sodium deoxycholate (NaDC) bridging toxicity studies; drug product formulation bridging toxicity studies; and impurity evaluations.

Overall, the results of the extensive nonclinical program encompassing pharmacologic, pharmacokinetic (PK), and toxicological evaluations support the safe use of ATX-101 at the

intended maximum dosage for improvement in the appearance of convexity or fullness associated with SMF in adults (Section 2.4).

Clinical Pharmacology

The physiologic homeostasis of bile acids is tightly regulated through several mechanisms, and their biology is well understood and documented. Exogenous DCA, administered as ATX-101, is indistinguishable from endogenous DCA and is regulated under the same homeostatic mechanisms. Thus, the elimination from the systemic circulation and the metabolic fate of DCA upon treatment with ATX-101 are identical to endogenous DCA. (Section 2.5).

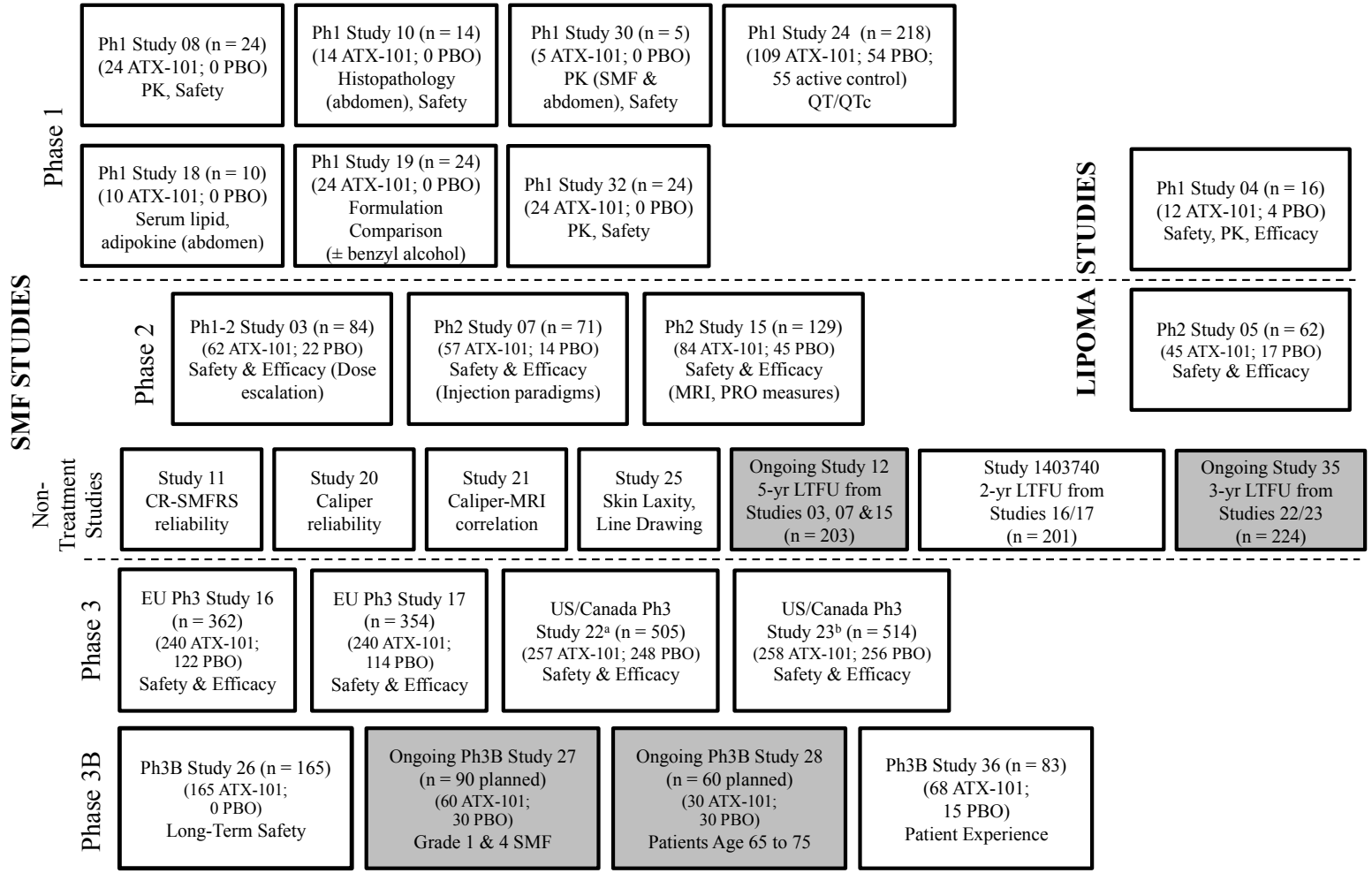
ATX-101 is injected directly in SC fat tissue, acts locally to physically disrupt the adipocyte cell membrane, and thus does not rely upon systemic distribution to exert its adipocytolytic effect. However, the PK of SC administration of ATX-101 into SMF were characterized in order to more fully understand the safety profile. Following a single SC injection of ATX-101 at the maximum intended dose of 100 mg, maximum observed plasma DCA concentrations (mean C_{max}) were seen within 1 hour (time to maximum observed plasma concentration [t_{max}]) and returned to the baseline endogenous DCA concentrations within 24 hours, indicating rapid absorption and subsequent clearance from the systemic circulation. At 100 mg, the systemic exposure of DCA, measured by C_{max} and area under the plasma concentration versus time curve from time 0 to 24 hours (AUC_{0-24}), was approximately 2- to 3-fold higher than average baseline endogenous exposure, yet still well within the range of normal baseline endogenous DCA levels and within levels typically observed postprandially. No relevant systemic side effects were observed with the transient DCA increase following ATX-101 administration. Considering the tight homeostasis of bile acids, the small ATX-101 dose (100 mg) equivalent to approximately 3% of the endogenous bile acid pool (~3 g) and the high intrinsic variability in baseline endogenous DCA levels, no intrinsic or extrinsic factors were determined to be of any clinical significance. ATX-101 has low potential for cytochrome P450 (CYP) inhibition, CYP induction, and transporter inhibition based on nonclinical in vitro studies; thus, no clinical drug-drug interaction studies were warranted and the potential impact of other drugs on DCA PK is small. Furthermore, because ATX-101 is a locally acting drug, systemic exposure (PK) is not related to the pharmacodynamics of the target indication.

Clinical Development Program

The clinical development program for ATX-101 includes 20 Phase 1-to-3 treatment studies, 18 of which directly investigated or supported the SMF indication and 2 of which investigated treatment of lipomas (Section 3.2). The SMF studies included patient populations relevant to the individual study objectives, representative of patients in the general population with undesired SMF, and who would be candidates for treatment with ATX-101. The Phase 2 program included dose-ranging studies that evaluated different concentrations and volumes of ATX-101, different injection pattern spacing, and different maximum numbers of treatment sessions. Results from these Phase 2 studies (Section 4.1) led to an optimal choice of dose and treatment regimen for pivotal Phase 3 Studies 22 and 23, which specifically evaluated 10 mg/mL ATX-101, injected at 1-cm spacing, for an area-adjusted dose of 2 mg/cm^2 (the recommended dose) relative to placebo (vehicle, including BA preservative, with the salt content increased slightly to provide comparable tonicity). Up to 10 mL ATX-101 per treatment session (ie, up to 100 mg DCA) was

given at intervals of not less than 4 weeks until the desired result was achieved, to a maximum of 6 treatment sessions. The pivotal studies (US/Canadian Phase 3 Studies 22 and 23) and primary supportive efficacy studies (EU Phase 3 Studies 16 and 17, and Phase 2 Study 15) were multicenter, blinded, randomized, and placebo-controlled, thus minimizing the effects of observer bias. Pivotal Studies 22 and 23 were independent (ie, no investigational center was included in both studies) but were identically designed, conducted, and analyzed, as were supportive Studies 16 and 17. An overview of all clinical studies (treatment and nontreatment) included in the ATX-101 clinical program with the number of patients exposed to ATX-101 per study is provided in Figure 1.

Figure 1: ATX-101 Clinical Program Overview



[a]The values for numbers of patients for Study 22 reflect the inclusion of Patient 124-009 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 4, when ATX-101 was administered in error.
[b]The values for numbers of patients for Study 23 reflect the inclusion of Patient 533-006 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 4, when ATX-101 was administered in error.
Notes: Numbers of patients reflect the Safety Analysis Population, ie, 2,664 total exposed: 1,698 ATX-101; 966 placebo/active control, and may differ from intent-to-treat population. Shaded boxes represent ongoing studies.

Efficacy

Efficacy Studies

The following 11 studies provide efficacy data relevant to ATX-101 for improvement in the appearance of moderate to severe submental convexity or fullness associated with SMF in adults (patient numbers represent the intent-to-treat [ITT] populations):

- 2 Phase 3 pivotal studies (Studies 22 and 23, total N = 1022)
- 2 Phase 3 supportive studies (Studies 16 and 17, total N = 721)
- 3 Phase 2 studies (Studies 03, 07, and 15, total N = 284)
- 1 Phase 3B open-label treatment and long-term follow-up (LTFU) study (Study 26, N = 165)
- 3 nontreatment LTFU studies (ongoing Study 12, N = 205 [subset of patients treated in Studies 03, 07, and 15], Study 1403740, N = 201 [subset of patients treated in Studies 16 and 17]), and ongoing Study 35, N = 224 [subset of patients treated in the pivotal Studies 22 and 23])

Studies 03 and 07 were the first studies of ATX-101 for SMF reduction. Study 03 was designed to evaluate different concentrations of ATX-101, with a fixed volume per injection and injection spacing. Alternatively, Study 07 used a fixed concentration of ATX-101, but varied injection volume and spacing. Phase 2 Study 15 was initiated next and, in addition to providing prospective data for the psychometric evaluation of the clinician-reported (CR) and patient-reported (PR) efficacy instruments, examined 2 concentrations of ATX-101 (5 and 10 mg/mL) to guide dose selection for pivotal studies. Supportive EU Phase 3 Studies 16 and 17 were initiated prior to knowledge of results from Study 15 and therefore included the same 2 concentrations of ATX-101 (5 and 10 mg/mL). Pivotal Studies 22 and 23 were subsequently conducted in the US and Canada and, based on results from Study 15, evaluated only the 10 mg/mL to-be-marketed concentration of ATX-101. Studies 26, 1403740, 35, and 12 were LTFU studies specifically designed to evaluate long-term maintenance of efficacy outcomes of ATX-101 at up to 1-, 2-, 3- and 5-years posttreatment, respectively (Section 4.4). Data from Study 35 were not yet available from this study at the time of ATX-101 New Drug Application (NDA) submission; therefore, no efficacy data are provided herein.

Endpoints

Throughout the ATX-101 clinical program, including the 2 identical, adequate and well-controlled Phase 3 studies conducted in the US and Canada (Studies 22 and 23), efficacy endpoints were rigorously collected and analyzed using appropriate, prespecified statistical methods. To evaluate the efficacy of ATX-101, clinician measures (Clinician-reported SMF Rating Scale [CR-SMFRS]), patient measures (Patient-reported SMF Rating and Impact Scales [PR-SMFRS and PR-SMFIS], Subject Self-Rating Scale [SSRS], and other endpoints) and objective measurements (SMF volume/thickness as measured by magnetic resonance imaging [MRI] and calipers) were employed in the clinical studies (Section 3.3). The clinician and patient measures are based on live assessments of the treatment area without reference to earlier

timepoints. All scales used as primary and secondary efficacy endpoints in the pivotal studies (ie, the CR-SMFRS, referred to as the clinician rating scale [Appendix A], PR-SMFRS, referred to as the patient rating scale [Appendix B], and PR-SMFIS, referred to as the impact scale [Appendix C]), were developed, evaluated, and documented in accordance with the FDA's Guidance document on Patient-Reported Outcome (PRO) Measures (FDA's PRO Guidance Document, 2009) and industry best practices. Of particular importance, the CR-SMFRS and PR-SMFRS used for primary efficacy endpoints in the pivotal studies are well-defined and reliable 5-point (0 to 4) instruments in which 1-grade improvements (or greater) have been established as being clinically meaningful based on their association with patient-reported impressions of at least moderate improvement in their SMF and high levels of patient satisfaction (Section 3.3.6). Good concordance has also been observed between SMF changes assessed by the clinician and patient rating scales.

To ensure that meaningful responses were observed from the perspectives of both the clinician and the patient, the 2 primary efficacy endpoints for the pivotal Phase 3 studies (22 and 23) incorporated composite SMFRS responses, which were defined as simultaneous improvements on both the clinician and patient rating scales. Both the 1-grade composite SMFRS response rate and a more stringent 2-grade composite SMFRS response rate were included as co-primary endpoints in the pivotal Phase 3 studies. Results from these studies confirmed previous assessments that both 2-grade and 1-grade composite SMFRS improvements are clinically meaningful.

Secondary endpoints in the pivotal Phase 3 studies were:

- MRI volume response rates evaluated in a subset of approximately 200 patients in each study, with a responder defined as having at least a 10% submental volume reduction in a prespecified region of interest from baseline to 12 weeks after the last treatment (as agreed upon with FDA; FDA Letter 16 December 2011; Section 3.3.5)
- change from baseline to 12 weeks after last treatment in the impact scale (PR-SMFIS) total scale score

In the interest of providing robust assurance that treatment with ATX-101 was resulting in clinically meaningful and interpretable reductions in SMF volume, and in consultation and agreement with the FDA, Kythera adopted a 10% change in SMF volume as the threshold for MRI response; this volume change is more closely associated with patients who reported that their SMF was "a great deal better" posttreatment. Regarding the PR-SMFIS total scale score, an approximately 3-point improvement in the impact scale is considered to be clinically meaningful based on association with moderate global improvement and a high level of patient satisfaction, both with treatment and with their appearance in relation to their face and chin.

Since patients may have received a different number of treatments due to varying amounts of SMF and/or desired improvement, primary efficacy evaluations were not conducted at a fixed time point relative to the start of study, but were determined relative to the last treatment received. The primary time point for efficacy in the pivotal studies, and in most supportive studies, was 12 weeks after the last treatment with ATX-101 or placebo. Efficacy assessments were also conducted at other time points, in order to describe the time-course and durability of responses.

The supportive EU Phase 3 studies also included 2 co-primary endpoints, which assessed the proportions of patients at 12 weeks after last treatment with: 1) at least 1-grade clinician rating scale response and 2) a SSRS rating (Appendix D) that indicated they were at least slightly satisfied with the appearance of their face and chin. These studies, along with Phase 2 Study 15, included the patient rating scale as a secondary endpoint, allowing for determinations of 1-grade and 2-grade composite clinician and patient scale responses comparable to pivotal Studies 22 and 23.

Patient Population

The clinical development program for ATX-101 included patient populations relevant to the individual study objectives, representative of patients in the general population with unwanted submental fullness, and who would be candidates for treatment with ATX-101. In particular, within the Phase 3 US/Canadian pivotal studies (22 and 23; Section 4.2.2), the enrolled population included:

- Male and female patients 18 to 65 years of age, with stable body weight, and body mass index (BMI) of ≤ 40 kg/m^2
- Patients with SMF rated by the investigator as 2 or 3 (ie, moderate or severe) on the CR-SMFRS, rated by the patient as 2 or 3 on the PR-SMFRS, and considered undesirable by the patient as characterized by a score of 0, 1, or 2 on the SSRS
- Patients with no prior intervention for SMF (eg, liposuction, surgery, or lipolytic agents), and without excessive skin laxity
- Patients without evidence of any cause of enlargement of the submental area other than SMF (eg, thyroid enlargement or cervical adenopathy) and without a history of trauma associated with the chin/neck that may affect evaluation of safety or efficacy
- Patients with stable body weight (in the judgment of the investigator) for at least 6 months and agreeing to refrain from making significant changes in dietary or exercise habits during the study
- Patients medically able to undergo the administration of study material (based on clinical physical exam and laboratory tests) and with no medical condition that would interfere with assessment of safety or efficacy or compromise the patient's ability to undergo study procedures or give informed consent

The demographic and baseline characteristics (Section 4.2.4) of the 1022 patients included in the ITT population of the pivotal Phase 3 studies (N = 506 in Study 22; N = 516 in Study 23) were similar across the individual studies and between treatment groups within each study. Further, the demographic and baseline characteristics of patients randomized to treatment in both studies are consistent with those of patients in the general population who would be expected to use ATX-101 in the commercial setting. In both studies, the ATX-101 and placebo treatment groups were well balanced; most patients were female (83.2% to 86.8%), white (85.2% to 90.8%) and not Hispanic/Latino (84.5% to 93.2%), with a mean age of 47.6 to 49.5 years, and a mean BMI of approximately 29 kg/m^2. The patients were evenly split between moderate (grade 2) and severe (grade 3) SMF as rated by the clinician using the CR-SMFRS.

In the pivotal Phase 3 studies, a similar percentage of patients in each treatment group completed the studies through the final follow-up visit (Visit 10) at 24 weeks after last treatment (82.9% to 88.3% for ATX-101 and 86.8% to 90.8% for placebo). The most common reasons for study discontinuation were patient convenience and loss to follow-up.

In both studies, a lower percentage of patients in the ATX-101 group than in the placebo group completed the maximum number of 6 treatments (53.9% to 64.1% for ATX-101 versus 77.1% to 85.2% for placebo). For the total of 211 patients in the ATX-101 group who received fewer than 6 treatment sessions across both studies, 2 of the most common reasons were related to efficacy. For 77 of the 211 patients (36.5%), the reason was insufficient remaining SMF and for 21 of the 211 patients (10.0%), the reason was patient satisfaction with SMF reduction. Other common reasons included AEs (36 ATX-101 patients; 6 placebo patients), withdrawal of consent for further treatments due to patient convenience (27 ATX-101 patients; 22 placebo patients) and loss to follow up (16 ATX-101 patients; 10 placebo patients).

Efficacy Results

Across studies, the efficacy results repeatedly demonstrated the superiority of ATX-101 relative to placebo in the reduction of SMF and other relevant outcomes. Consistent improvement in the appearance of moderate to severe convexity or fullness associated with SMF is observed from the perspective of the clinician, the patient, and objective measurements using MRI and calipers, and these observable improvements have a positive impact on the patient. The key efficacy results (Section 4.2.5) and conclusions (Section 4.5) are summarized below.

Primary Endpoints

Pivotal Phase 3 Studies 22 and 23 each met their co-primary efficacy endpoints: the 1-grade composite SMFRS response rate (ie, proportion of patients with at least 1-grade simultaneous improvement on both the CR-SMFRS and the PR-SMFRS) and 2-grade composite SMFRS response rate (ie, proportion of patients with at least 2-grade simultaneous improvement in both the CR-SMFRS and the PR-SMFRS) at 12 weeks after last treatment. Specifically:

- In Study 22, a 1-grade composite SMFRS response (or greater) was obtained in 70.0% of ATX-101-treated patients compared with 18.6% of placebo-treated patients ($p < 0.001$). A 2-grade composite SMFRS response was obtained in 13.4% of ATX-101-treated patients in Study 22 compared with no placebo-treated patients ($p < 0.001$; Table 1).
- In Study 23, a 1-grade composite SMFRS response was obtained in 66.5% of ATX-101-treated patients compared with 22.2% of placebo-treated patients ($p < 0.001$). A 2-grade composite SMFRS response was obtained in 18.6% of ATX-101-treated patients in Study 23 compared with 3.0% of placebo-treated patients ($p < 0.001$; Table 1).

Table 1: Co-primary Efficacy Results – Pivotal Studies 22 and 23

Co-primary Endpoints (12 weeks after last treatment)	Study 22		Study 23	
	Placebo N = 250	ATX-101 N = 256	Placebo N = 258	ATX-101 N = 258
1-Grade Composite SMFRS				
Responder, n	47	179	57	171
(%)	(18.6)	(70.0)	(22.2)	(66.5)
p-value		< 0.001		< 0.001
2-Grade Composite SMFRS				
Responder, n	0	34	8	48
(%)		(13.4)	(3.0)	(18.6)
p-value		< 0.001		< 0.001

ATX-101 = deoxycholic acid injection; SMFRS = Submental Fat Rating Scale.
Note: Results shown are for protocol-specified co-primary analyses based on intent-to-treat (ITT) datasets consisting of all randomized patients.
Source: Table 1, Section 2.5 of NDA 206333

Secondary Endpoints

Magnetic Resonance Imaging

Pivotal Phase 3 Studies 22 and 23 each met their secondary efficacy endpoint related to SMF volume reduction as assessed by MRI (Section 4.2.5.2.1). Based on MRI assessments, 46.3% and 40.2% of ATX-101-treated patients were considered MRI responders (ie, exhibited at least a 10% reduction in SMF volume from baseline to 12 weeks after the last treatment) in Studies 22 and 23, respectively, compared with 5.3% and 5.2% of patients treated with placebo (all $p < 0.001$; Table 2).

Patient Reported SMF Impact Scale (PR-SMFIS)

The pivotal Phase 3 studies also met their secondary efficacy endpoint related to self-rated visual and emotional impacts of SMF (ie, how happy, bothered, self-conscious, embarrassed, older looking or overweight the patient felt due to the appearance of their "chin fat"; Section 4.2.5.2.2). In both Study 22 and Study 23, treatment with ATX-101 significantly reduced (improved) the PR-SMFIS total scale score from baseline to 12 weeks posttreatment compared with placebo. Specifically,

- In Study 22, the least squares (LS) mean change from baseline was -3.61 for ATX-101 vs -1.10 for placebo, which represents an approximately 50% reduction (improvement from baseline) for ATX-101 compared with a 15% reduction for placebo ($p < 0.001$; Table 2).
- In Study 23, the LS mean change from baseline was -3.44 for ATX-101 vs -1.46 for placebo, which represents an approximately 47% reduction (improvement from baseline) for ATX-101 compared with a 20% reduction for placebo ($p < 0.001$; Table 2).

Additionally, the patients treated with ATX-101 had a mean change that is greater than the 3-point improvement in impact scale that was established as clinically meaningful

(Section 3.3.6), whereas patients treated with placebo did not. Results for the individual component items of the PR-SMFIS were evaluated using observed data and, in both Studies 22 and 23, each of the 6 items demonstrated improvement in patients treated with ATX-101 compared to those treated with placebo.

Table 2: Secondary Efficacy Results – Pivotal Studies 22 and 23

Secondary Endpoints (12 weeks after last treatment)	Study 22		Study 23	
	Placebo N = 250	ATX-101 N = 256	Placebo N = 258	ATX-101 N = 258
MRI Volume (≥ 10% decrease), N[a]	111	113	112	113
Responder, n	6	52	6	45
(%)	(5.3)	(46.3)	(5.2)	(40.2)
p-value		< 0.001		< 0.001
PR-SMFIS total scale score				
Mean at baseline	7.33	7.17	7.24	7.37
(SD)	(1.62)	(1.69)	(1.68)	(1.72)
LS mean change from baseline	-1.10	-3.61	-1.46	-3.44
(SE)	(0.143)	(0.143)	(0.156)	(0.158)
p-value		< 0.001		< 0.001

ATX-101 = deoxycholic acid injection; LS = least squares; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; SD = standard deviation; SE = standard error
[a] Evaluated in subset of patients who underwent MRI evaluations (ITT-MRI dataset)
Note: Results shown are based on intent-to-treat (ITT) datasets consisting of all randomized patients.
Source: Integrated Summary of Efficacy Tables 11 and 12 in NDA 206333

Additional Endpoints

Additional prospective efficacy endpoints in pivotal Phase 3 Studies 22 and 23 included evaluations of co-primary and secondary endpoints at alternate timepoints (eg, 24 weeks after last treatment [Visit 10]) and evaluations of changes in the CR-SMFRS, PR-SMFRS and MRI volume as continuous measures. Other measures of efficacy were also included as prospective endpoints, including patient satisfaction with the appearance of their face/chin based on the SSRS, patient assessments of SMF based on line drawings representing each grade (ie, the Patient-Reported Submental Fat Line Drawing [PR-SMF-LD] ratings), thickness of SMF measured using calipers and by MRI, and Global Questions regarding improvement in SMF, improvement in chin/neck definition, and treatment satisfaction. All of these endpoints and analyses were specified in the protocols for Studies 22 and 23 and they provide important corroborating information that supports the efficacy and benefits of ATX-101. In every analysis, the results of the additional endpoints supported the conclusions drawn from the co-primary and secondary endpoint analyses, and further confirmed the superiority and benefits of ATX-101 relative to placebo in reducing SMF (Section 4.2.5.3).

Persistence of Efficacy and/or Tolerance Effects

The mechanism of action of ATX-101 (Section 2.2) suggests that its effects will be long-lasting and that retreatment of SMF is unlikely to be necessary. This conclusion is further supported by

the persistence of efficacy (ie, maintenance of response) observed in LTFU of patients treated with ATX-101 in clinical studies. In addition to the 24-week posttreatment data from pivotal Studies 22 and 23 (Section 4.2.5.3), such LTFU efficacy results are available from Studies 26, 1403740, and 12 (Section 4.4), which were specifically designed to evaluate long-term maintenance of efficacy outcomes of ATX-101 at up to 1-, 2-, and 5-years posttreatment, respectively. Data from ongoing Study 35, a nontreatment study collecting LTFU data for up to 3 years after the last treatment in a subset of patients who participated in the pivotal Phase 3 Studies 22 and 23, were not yet available from this study at the time of ATX-101 NDA submission; therefore, no data are provided herein.

Persistence of efficacy was primarily analyzed based on the proportion of responders at 12 weeks after last treatment (eg, in the predecessor study for patients in Study 12 and Study 1403740) who were still responders at the LTFU timepoint being examined. For this purpose, responders were considered based on 1-grade improvements in the CR-SMFRS, PR-SMFRS and the composite SMFRS. Note that early Studies 03 and 07 did not include the PR-SMFRS, so PR-SMFRS and composite SMFRS results for Study 12 are derived solely from patients treated in later Phase 2 Study 15. It should also be noted that the analyses in the 3 studies differed in that the denominators in Study 26, which included both treatment and LTFU, were based on the numbers of responding patients in the study (regardless of whether they attended the assessment visit), while the denominators in Studies 12 and 1403740 were based on the numbers of responding patients who attended the assessment visit, since not all patients in the predecessor studies consented to enrollment in Studies 12 and 1403740 and not all patients attended (or would have been eligible to attend) every visit.

Nonetheless, the results from the 3 studies were comparable and showed a high persistence of efficacy over time. Specifically, at the 1-year timepoint common to all studies, the maintenance of a 1-grade CR-SMFRS response was 90.4% (113 of 125 patients) in Study 26; 85.0% (34 of 40 patients) and 87.0% (47 of 54 patients) for patients who previously received 1 mg/cm^2 and 2 mg/cm^2 ATX-101, respectively, in Study 1403740; and 93.9% (77 of 82 patients) in Study 12. Similarly, at 2 years posttreatment, 90.0% (36 of 40 patients) and 87.0% (47 of 54 patients) of patients in Study 1403740 who previously received 1 mg/cm^2 ATX-101 and 2 mg/cm^2 ATX-101, respectively; and 91.7% (66 of 72 patients) in ongoing Study 12 maintained their 1-grade CR-SMFRS response. In Study 12, in which patients are to be followed for up to 5 years, the maintenance of a 1-grade CR-SMFRS response was 80.4% (41 of 51 patients) and 87.9% (29 of 33 patients) at the 3- and 4-year timepoints, respectively (Table 19).

Overall, based on the mechanism of action of ATX-101, the analyses conducted 24 weeks after the last treatment session in the pivotal Phase 3 studies, and the results of LTFU in Studies 26, 1403470, and 12, it can be concluded that reductions in SMF following treatment with ATX-101 are sustained and have been maintained for up to 4 years.

Safety

Safety Studies

The safety of ATX-101 was evaluated in 23 Phase 1 to Phase 3 clinical studies, 19 of which support the SMF indication (Figure 1). Of the 19 SMF studies, 16 are included in the integrated safety dataset:

- 2 pivotal Phase 3 studies (Studies 22 and 23, N = 1019)
- 2 supportive Phase 3 studies (Studies 16 and 17, N = 716)
- 3 Phase 2 studies (Studies 03, 07, and 15, N = 284)
- 5 Phase 1 studies (Studies 08, 19, 24, 30, and 32, N = 295)
- 4 LTFU studies (nontreatment Study 12, N = 203 [subset of patients treated in Studies 03, 07 and 15], nontreatment Study 1403740, N = 201 [subset of patients treated in Studies 16 and 17], nontreatment Study 35, N = 224 [subset of patients treated in the pivotal Studies 22 and 23], and open-label treatment and LTFU Study 26, N = 165)

The other 3 studies contributing to the safety database are Phase 3B Studies 27 and 28 that are ongoing and blinded, and recently completed Phase 3B Study 36. Individual safety summaries from these studies were presented in the 120-Day Safety Update and Study 36 patients are included in the updated exposure numbers herein (Table 20).

Endpoints

The safety evaluation program for ATX-101 included both spontaneously reported and elicited adverse events (AE), acute and late-onset events, electrocardiograms (ECG), and clinical laboratory evaluations. Particular attention was also given to a large set of AEs of special interest (AESI) that might be expected to occur given the mode of administration (injection), mechanism of drug action, or the resulting local tissue response.

Patient Population

Of the 2664 patients participating in the 18 completed treatment studies, 1698 were treated with ATX-101, 911 were treated with placebo, and 55 were treated with active control (for evaluation of QT interval prolongation in Study 24). Over 700 patients have been exposed to up to 6 monthly treatments with ATX-101 at the 2 mg/cm^2 dosage intended for clinical use (see Studies 22, 23, 26 and 15 in Table 20).

The safety population for the randomized, double-blind, placebo controlled pivotal Phase 3 Studies 22 and 23 included all patients who received at least 1 dose of study drug (ATX-101 or placebo) and all patients were analyzed according to the treatment actually received, regardless of randomized treatment assignment. The pivotal studies pooling group consists of all patients treated in Studies 22 and 23, which were conducted according to identical protocols in the US and Canada. Results for the pivotal studies and the pooled pivotal data are considered most informative for the assessment of safety.

Table 21 summarizes exposure to ATX-101 in the pivotal studies. Most patients (81.2%) in the placebo group received the maximum number of treatment sessions (6), whereas a substantially lower percentage of patients (59.0%) in the ATX-101 group underwent 6 treatments. Consistent with this observation, the median total volume of study drug injected over the course of treatment was also lower in the ATX-101 group (24.2 mL) than in the placebo group (33.6 mL). The median total amount of DCA received by the ATX-101 group was 242.0 mg, which is substantially lower than the maximum amount allowed over the course of 6 treatments (600 mg).

Safety Results

Across the clinical development program, treatment with ATX-101 was safe and well tolerated. Individual and pooled results from pivotal Phase 3 Studies 22 and 23 are indicative of the overall safety profile of ATX-101. Safety data from these studies are also consistent with results observed in previous ATX-101 studies. Although some small differences in incidence of AEs were noted, the types, incidences, duration, and severity of AEs were generally similar regardless of demographics or baseline characteristics.

As expected for a facial injectable product, AEs associated with treatment were reported in most patients in both treatment groups (97.3% ATX-101; 89.7% placebo) and were predominantly local reactions in the treatment area (reported in 94.6% of patients treated with ATX-101 and 77.4% of patients treated with placebo). These AEs were usually transient and resolved within the treatment interval; 82% of AEs in the ATX-101 group and 89% of AEs in the placebo group resolved within 30 days. Most AEs were mild or moderate in severity (98% of events in ATX-101 patients; 99% of events in placebo patients), and typically required no action to be taken for the event to resolve (88% of events in ATX-101 patients; 85% of events in placebo patients). Adverse events not associated with the treatment area, including systemic events, and judged to be related to study drug were uncommon and typically not serious or severe. In the pivotal studies, serious adverse events (SAEs) were reported in 2.5% of patients treated with ATX-101 and 4.4% of patients treated with placebo. None of these SAEs were reported to be related to study drug.

The most frequently reported AEs in the pivotal studies were local reactions at the injection site including hematoma (predominantly reported as bruising), pain, anesthesia, edema, swelling, erythema, induration, paresthesia, nodule, and pruritus (Table 3 [pooled data ≥ 5%]; Table 23 [pooled data ≥ 2%]). These local reactions are expected based on the mode of administration (local injection), the pharmacologic action of ATX-101, and the resulting tissue response. Adverse events not associated with the treatment area, including systemic events, were uncommon, typically not serious (Section 5.3.7) or severe (Section 5.3.5), tended to be distributed among a range of system organ classes (SOCs) and did not exhibit a pattern that would indicate the existence of a relationship with ATX-101.

Table 3: Most Common (Frequency ≥ 5% in ATX-101 Group) Preferred Terms of Adverse Events – Pooled Pivotal Studies 22 and 23

Preferred Term	Placebo N = 504 n (%)	ATX-101 N = 515 n (%)
Injection site hematoma	353 (70.0)	368 (71.5)
Injection site pain	158 (31.3)	358 (69.5)
Injection site anesthesia	29 (5.8)	341 (66.2)
Injection site edema	147 (29.2)	311 (60.4)
Injection site swelling	79 (15.7)	171 (33.2)
Injection site erythema	90 (17.9)	137 (26.6)
Injection site induration	13 (2.6)	120 (23.3)
Injection site paresthesia	19 (3.8)	71 (13.8)
Injection site nodule	13 (2.6)	69 (13.4)
Injection site pruritus	30 (6.0)	64 (12.4)
Headache	19 (3.8)	42 (8.2)
Nasopharyngitis	39 (7.7)	35 (6.8)

ATX-101 = deoxycholic acid injection
Notes: Preferred terms are displayed in decreasing order of frequency in the ATX-101 group and were based on MedDRA Version 14.1. Patients experiencing more than 1 AE for a preferred term were counted only once for that preferred term. The frequency cut-off for each preferred term was calculated as follows: (number of patients receiving ATX-101 with an event) / (all patients receiving ATX-101 in the study pooling group) x 100.
Source: Table 17, Section 2.7.4.2.3.1.1 of NDA 206333

Although similar AEs were reported in patients treated with both placebo and ATX-101, given the common occurrence of local treatment reactions that had a higher incidence in the ATX-101 group, coupled with strong efficacy, may have inadvertently introduced some clinician or patient bias. Objective MRI assessments, which are not subject to such bias, confirm the efficacy results and a demonstrable treatment effect, as does the overall comprehensive assessment of the data.

There were 2 reported deaths (Section 5.3.8) in the pivotal studies (road traffic accident in a patient treated with ATX-101 and heroin toxicity in a patient treated with placebo [preferred term = toxicity to various agents]). There were an additional 2 deaths in the overall ATX-101 SMF development program: cardiac arrest and cardiac death, both of which occurred in patients who received 2 mg/cm^2 ATX-101. No death was considered by the investigator to be related to study drug. The 2 cardiac deaths occurred > 140 days after the last treatment.

Adverse events of special interest (Section 5.3.11) were prespecified based on events observed in earlier studies. The AESI categories were constructed in a fashion that would group together similar preferred terms (ie, those describing similar events, for example swelling and edema) to better identify and characterize common AEs/reactions. Of note, motor nerve injury and ulceration were identified as special interest AEs likely to be related to incorrect injection procedure or technique; either injection placement outside of the submental region or failure to inject midlevel into SC fat. These 2 AESI categories are further discussed below, along with dysphagia, which was observed in 1.9% of patients treated with ATX-101 in the pivotal studies.

Injection Site Motor Nerve Injury

Motor nerve injury (Section 5.3.11.1) describes events consistent with motor neuropraxia (presents as an asymmetrical smile), suggesting irritation or injury of the marginal mandibular branch of the facial nerve. The marginal mandibular branch of the facial nerve courses superficially across the mandible just outside of the SMF region but is adjacent to the external border of the potential treatment area (within a 3-cm radius circle centered at a point approximately 2 cm lateral to and 2 cm inferior to the oral commissure). In the pivotal studies, injection site nerve injury was reported in 22 patients (4.3%; 23 events) in the ATX-101 group and 2 patients (0.4%; 2 events) in the placebo group. Most events were mild or moderate in severity, with 1 patient (0.2%) in the ATX-101 group and no patients in the placebo group reporting severe events. Injection site nerve injury had a median duration of 42 days in the ATX-101 group and 85 days in the placebo group. All of these nerve injury events were temporary and recovered/resolved without sequelae.

In the broader safety population of all SMF studies in the development program, there were 39 events of injection site nerve injury reported in 30 patients (2.9%) in the ATX-101 2 mg/cm^2 group and 3 events reported in 3 patients (0.3%) in the placebo group. Of note, the attempt to capture any potential motor nerve injury event resulted in the inclusion of 4 patients who did not have nerve injury events related to the region of interest, ie, the marginal mandibular nerve (3 pinched nerves [2 ATX-101 2 mg/cm^2 and 1 placebo] and 1 report of thumb weakness in a patient treated with ATX-101 at >2 mg/cm^2).

To reduce the potential for motor neuropraxia of the marginal mandibular nerve, injection above the inferior aspect of the mandible, or within the region defined by the 3-cm radius circle described above, is not advised.

Skin Ulceration

Skin ulceration (Section 5.3.11.2) describes events of small (typically 3-5 mm) superficial erosions of the skin/dermis at injection sites within the treatment area. These events are consistent with either shallow injections superficial to the SC fat (ie, into the skin/dermis) or continued injection during needle withdrawal. The only treatment area skin ulceration (erosion) event observed in the pivotal studies (and across all of the placebo-controlled SMF studies) occurred in a 53-year-old male in Study 23 during his last treatment session. The event lasted 23 days and resolved without sequelae. Two patients in the nonpivotal placebo-controlled studies (1 each for ATX-101 and placebo) had ulceration events unrelated to treatment or the region of interest (both gluteal lesions). In open-label Phase 3B Study 26, 4 study-drug-related events of injection site skin ulceration were reported (in addition to 1 event unrelated to study drug). The 4 events were mild or moderate, had median durations of 13 to 26 days and also resolved without sequelae.

Across the SMF development program, the overall incidence of study-drug-related skin ulcerations in patients treated with 2 mg/m^2 ATX-101 was 0.5% (5/1050). No severe skin ulceration events were reported for either ATX-101 or placebo patients across the clinical development program. All of the events were reported as recovered/resolved. The few ulceration events reported occurred randomly with respect to treatment session.

To reduce the potential for superficial skin ulceration, injection of ATX-101 should be delivered midway into the SC fat layer and should not be continued during withdrawal of the syringe from the skin.

Dysphagia

Dysphagia (Section 5.3.11.3) describes events consistent with patient reports of discomfort/difficulty with swallowing. The sensation of dysphagia is attributable to a sensation of fullness in the submental/neck area associated with post injection swelling/edema. In addition to spontaneous reporting of such events by patients, investigators also elicited whether dysphagia symptoms were experienced during treatment.

In the pivotal studies, dysphagia was reported in 10 patients (1.9%; 10 events) in the ATX-101 group and 1 patient (0.2%; 1 event) in the placebo group. Most events were mild, with 2 patients (0.4%) in the ATX-101 group reporting severe events. Subject 23-514-002 reported severe dysphagia with onset 5 days after the first treatment session. The patient received fewer than 6 treatments and discontinued from the study; the event resolved. Subject 23-528-016 reported severe dysphagia with onset 1 day after the fourth treatment session; the event resolved in 2 days. The patient continued to receive additional treatment and completed the study. Overall, events of dysphagia were reported in a small proportion (1% to 2%) of patients treated with ATX-101, were usually mild in severity, and typically resolved within a few days.

Other Observations Related to Safety

Long-term safety data (Section 5.4.1) are available from Study 12 (ie, patients previously treated in Phase 2 Studies 03 [n = 56], 07 [n = 58] or 15 [n = 91]), Study 1403740 (ie, patients previously treated in EU Phase 3 Studies 16 [n = 101] or 17 [n = 100]), Study 35 (ie, patients previously treated in pivotal Studies 22 [n = 120] and 23 [n = 104]), and open-label treatment and LTFU Study 26 (n = 137 patients who completed Visit 10). Adverse events that started during the LTFU period were reported in 36 patients (9.6%) in the ATX-101 2 mg/cm^2 group and 7 patients (2.9%) in the placebo group. The only individual AEs that started during the LTFU period and were reported in more than 1 patient treated with ATX-101 (2 mg/cm^2) were hypertension (3 patients [0.8%]), hypothyroidism (2 patients [0.5%]), nasopharyngitis (2 patients [0.5%]), and sinusitis (2 patients [0.5%]). No AE that started during the LTFU period was reported in more than 1 patient in the placebo group. No new safety concerns or signals were identified during the LTFU period (ie, up to 4 years posttreatment).

Treatment with ATX-101 was not associated with any clinically meaningful changes in liver function tests, renal function tests, serum lipid concentrations, or hematology results (Section 5.4.2). Study 24 was designed specifically to evaluate the cardiac effects of ATX-101, at both therapeutic (100-mg dose) and supratherapeutic (200-mg dose) doses, by measurement of the time from the beginning of QRS complex to the end of T wave (QT/corrected QT [QTc]) intervals in healthy volunteers, with both moxifloxacin and placebo as controls. ATX-101 had no effect on QT/QTc intervals, and no cardiac safety concerns were identified.

Despite the majority of patients having reductions in SMF volume, > 90.0% of patients in the pivotal studies were reported to have improved or unchanged skin laxity scores at 12 weeks after last treatment, compared with baseline, based on the Submental Skin Laxity Grade (SMSLG)

scale (Section 5.4.3). It can therefore be concluded that reductions in SMF due to ATX-101 do not result in adverse impacts on skin laxity.

Risk Management Plan

The Sponsor intends to mitigate risk (Section 7) by providing detailed product labeling that will inform health care providers on injection site risks and emphasize techniques to avoid or reduce injection site AEs (eg, neuropraxia, ulceration). In addition, the Sponsor intends to offer comprehensive prescriber injection training to inform physicians on the correct use of ATX-101 in appropriate patients with undesired SMF. Routine pharmacovigilance and monitoring of AEs from the global safety database, as well as postmarketing surveillance to monitor for any rare, but clinically relevant AEs is planned. Details of risk management are presented below.

To ensure adequate oversight of any potential safety concerns associated with ATX-101, Kythera has included sufficient information regarding directions for use and associated risks in the product labeling to allow for the safe use of ATX-101 in the postmarketing setting. Topics covered include the selection of appropriate patients, use of the correct number and locations for injections, proper administration techniques, and pain management options. Prescribers are instructed to screen for other causes of submental fullness such as thyromegaly and cervical lymphadenopathy, and are also advised to carefully consider patients with excessive skin laxity, prominent platysmal bands, scar tissue, prior surgical or aesthetic procedures in the treatment area, or other conditions for which reduction of SMF may result in an aesthetically undesirable outcome. Caution is advised in cases where patients have a history of dysphagia or facial neuropraxia, or have inflammation or induration at the treatment area.

Injection technique is outlined in the package insert, such as injecting perpendicular to the skin surface, mid-way into the SC fat and not injecting during withdrawal of the syringe to avoid superficial injections into the dermis that may lead to ulceration or inadvertent injection into salivary glands, lymph nodes, or muscles. Detailed directions are provided to decrease the risk for motor neuropraxia (of the marginal mandibular nerve), including avoiding injection above the inferior border of the mandible and within a 3-cm radius circle centered at a point approximately 2 cm lateral to and 2 cm inferior to the oral commissure.

In addition to what is provided in the package insert, an injection training program will be offered to physicians in multiple formats, including web-based and/or live sessions at educational meetings or the physician's office. This training will include a detailed review of cervicomental anatomy and thorough demonstrations of patient assessment, ATX-101 injection technique, and patient comfort management. The effectiveness of the injection technique training will be assessed periodically and modified as appropriate. For example, an injection training video will be used to demonstrate the correct clinical procedures, including proper injection technique, for the administration of ATX-101.

In order to develop an understanding of the condition of submental fullness due to SMF, how it is treated in current clinical practice, and the risks and benefits associated with its treatment, Kythera is planning to conduct a prospective, observational, multicenter registry study (Study ATX-101-15-40M; Condition of Submental Fullness and Treatment Outcomes Registry [CONTOUR]). This registry will involve the systematic collection of data on the population of physicians with patients who have SMF concerns, the population of patients who are

eligible for SMF reduction treatment, eligible patients who elect SMF reduction treatment, treatment procedures, and treatment outcomes.

Benefit-Risk Analysis

No drug product has been registered for the reduction of localized fat deposits in the US. Current treatment options for reduction of SMF include traditional aesthetic surgical procedures performed under general anesthesia, as well as targeted liposuction, which may be performed under general or local anesthesia. In the absence of an approved drug product, extemporaneous, non-GMP pharmacy-compounded PC/DC mixtures have been used by many practitioners and may incur risks related to the assurance of appropriate strength, sterility, and consistency. Treatment with ATX-101 represents a nonsurgical, in-office procedure for SMF reduction, with no need for general anesthesia, and serves as a minimally-invasive, safe, and clinically-proven regulated alternative to unregulated, compounded, and misbranded lipolytic products with unknown quality, safety, and efficacy.

The results from 2 identical, adequate and well-controlled Phase 3 studies conducted in the US and Canada (Studies 22 and 23) demonstrated that ATX-101, when administered at the recommended dose of 2 mg/cm^2 for up to 6 treatments at 4-week intervals, was superior to placebo for the reduction of SMF and improvement in the appearance of submental fullness, as assessed by clinician (CR-SMFRS), patient (PR-SMFRS, PR-SMFIS, etc.), and objective measures (MRI and calipers). Consistent and long-lasting improvements in SMF were documented across studies in the clinical program and these observable improvements had a positive impact on patient self-perceptions and led to a high degree of patient satisfaction. Furthermore, the effects of ATX-101 on the reduction of SMF are durable and have been maintained for at least 4 years following treatment. The total dose in each treatment session and the overall number of treatments are both tailored to the individual patient based on the amount and distribution of SMF, as well as the patient's desired result.

The safety profile of ATX-101, when used in adults for improvement in the appearance of convexity or fullness associated with SMF, is well characterized. Results from pivotal Phase 3 Studies 22 and 23 establish the overall safety profile of ATX-101, and are consistent with results observed in previous ATX-101 studies. ATX-101 is an acute, elective, and safe treatment, with mostly transient and mild or moderate AEs related to the treatment area that resolve without intervention or sequelae, and that can be readily managed by the practitioner. No long-term safety issues associated with ATX-101 treatment have been identified to date. Furthermore, the types of AEs observed during LTFU were infrequent in occurrence, mild in severity, and in general similar to those observed in the pivotal studies, with an expected lower incidence of study-drug or treatment area-related AEs.

Based on the safety profile of ATX-101 characterized by transient and mostly mild or moderate AEs related to the treatment area, it is reasonable that patients, in consultation with their physicians, will be able to weigh the benefits and risks of treatment with ATX-101 on an ongoing basis and decide whether or not to initiate and/or continue additional treatment without putting the patient at undue risk.

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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse event(s) of special interest
ANCOVA	analysis of covariance
ATX-101	deoxycholic acid injection
AUC_{0-24}	area under the plasma concentration versus time curve (from time 0 to 24 hours)
AUC_{0-last}	area under the plasma concentration versus time curve (from time 0 to last)
BA	benzyl alcohol
BLOQ	below the limit of quantitation
BMI	body mass index
CL	clearance or apparent clearance
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CR	clinician-reported
CR-SMFRS	Clinician-Reported Submental Fat Rating Scale
CYP	cytochrome P450
DC	deoxycholate (from either deoxycholic acid or the sodium salt)
DCA	deoxycholic acid
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GMP	good manufacturing practice
HPLC	high-performance liquid chromatography
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
hERG	human ether-a-go-go-related gene
IC_{50}	fifty percent inhibitory concentration
ICH	International Conference on Harmonisation
ITT	intent-to-treat
ITT-MRI	subset of ITT population who were enrolled to undergo MRI assessment
LC_{50}	median lethal concentration
LOCF	last observation carried forward
LS	least squares

Abbreviation/Term	Definition
LSM	least squares mean(s)
LTFU	long-term follow-up
MI	multiple imputation(s) or multiply imputed
MRI	magnetic resonance imaging
NaCl	sodium chloride
NaDC	sodium deoxycholate
Na_2HPO_4	dibasic sodium phosphate
NDA	new drug application
NOAEL	no observed adverse effect level
NTCP	sodium-taurocholate cotransporting polypeptide
PBS	phosphate-buffered saline
PC	phosphatidylcholine
PGIC	patient global impression of change
PK	pharmacokinetic(s)
PR	patient-reported
PRO	patient-reported outcome
PR-SMFIS	Patient-Reported Submental Fat Impact Scale
PR-SMF-LD	Patient-Reported Submental Fat Line Drawing
PR-SMFRS	Patient-Reported Submental Fat Rating Scale
QT	interval, time from beginning of QRS complex to end of T wave
QTc	corrected QT interval
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SMF	submental fat
SMFRS	Submental Fat Rating Scale (composite of CR-SMFRS and PR-SMFRS)
SMSLG	Submental Skin Laxity Grade
SOC	system organ class
SRA	Self-Ratings of Attractiveness
SSRS	Subject Self-Rating Scale
SUSAR	suspected, unexpected, serious adverse reaction
SWFI	sterile water for injection
$t_{½}$	terminal elimination half-life

Abbreviation/Term	Definition
t_{max}	time to maximum observed plasma concentration
TK	toxicokinetic
TQT	thorough QT
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
US	United States
V	volume of distribution of the central compartment
WFI	water for injection

2. OVERVIEW OF PRODUCT

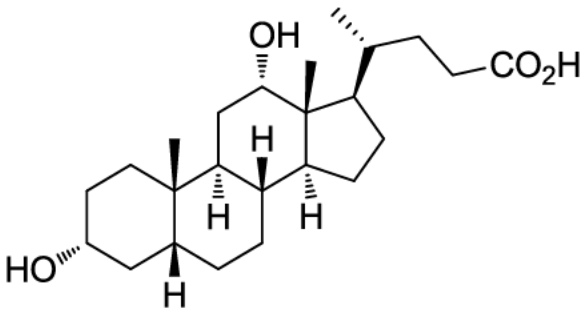
2.1. Description of Molecule

Endogenous DC is a secondary bile acid formed from cholate by bacterial action (Norman and Shorb, 1962) and serves to solubilize dietary fat, thereby aiding in its absorption in the gut. Produced in the gastrointestinal tract, it is one of several end products of cholesterol metabolism; DC does not undergo subsequent degradative catabolism. It is absorbed in the gut where it rejoins the enterohepatic circulation or is excreted intact in the feces (Dawson, 2002; Street et al., 1983). Endogenous DC is quantifiable in the peripheral circulation in animals and man and steady-state levels vary by species and fed/fasted status. As exogenously administered DC from synthetic DCA and endogenous DC are biologically identical, the terms deoxycholic acid and deoxycholate may be used interchangeably.

The nonclinical development program and early clinical studies were completed using ATX-101 containing NaDC purified from bovine and ovine bile. Subsequent process development and manufacturing changes enabled the chemical synthesis of deoxycholic acid (synthetic DCA), which was of a higher purity and avoided the risk of xenotropic pathogens, including viruses and prions associated with transmissible spongiform encephalopathies. Deoxycholate from synthetic and animal-derived sources were demonstrated to be structurally identical in solution and of comparable high quality; bridging toxicology studies also did not identify any differences.

ATX-101 is an injectable drug product that consists of DCA (3α,12α-dihydroxy-5β-cholan-24-oic acid; Figure 2) drug substance formulated in a sterile solution of dibasic sodium phosphate (Na_2HPO_4), sodium chloride (NaCl) and water for injection (WFI), with BA as a preservative, pH = 8.3. The placebo drug product used in clinical studies was manufactured using the same formulation as ATX-101, including BA preservative and with the salt content increased slightly to provide comparable tonicity, but without DCA.

Figure 2: Molecular Structure of Deoxycholic Acid



2.2. Mechanism of Action

The mechanism of action of ATX-101 is supported by Phase 1 clinical histology data (Study 10), as well as in vitro and in vivo nonclinical studies. When ATX-101 is injected into localized SC fat, DCA physically disrupts the cell membrane of adipocytes and causes adipocytolysis, the destruction of fat cells. The destruction of adipocytes elicits a predictable tissue response in which macrophages are attracted to the area to eliminate cellular debris and lipids, which are

then cleared through natural processes. This is followed by the appearance of fibroblasts and observed thickening of fibrous septa suggesting an increase in total collagen (ie, neocollagenesis). The activity of DCA is attenuated by protein, making protein-poor tissues, such as SC fat, more susceptible to its cytolytic effects. Thus, when injected into fat tissue, nearby protein-rich tissues such as skin and muscle are largely unaffected.

Results from Study 10 demonstrate that dosing with ATX-101 (all dosing paradigms) resulted in histological changes confined to SC fat; no changes were observed in the dermis or epidermis following treatment. Immediate focal adipocytolysis was observed, followed by the expected inflammatory tissue response (primarily consisting of neutrophils early on at Days 1 to 3 and then macrophage infiltration to remove cellular debris) and finally a resolution of inflammation and resulting thickening of the fibrous septae. The time course of adipocytolysis and the acute inflammatory response observed in Study 10 supports the recommended ATX-101 dosing interval of not less than every 4 weeks.

Study 18 was a single-center, open-label, fixed-dose 2-stage study to evaluate the lipid and adipokine profiles following SC injection of ATX-101 into abdominal fat tissue in otherwise healthy adults. Results from this study demonstrate that administration of ATX-101 and the induced adipocytolysis results in a transient elevation of serum free fatty acids, which is within the range of DCA values observed following a meal. Adipocytolysis induced by ATX-101 did not result in clinically meaningful effects or trends outside of the normal range on serum lipids or adipokines.

2.3. Treatment Regimen

ATX-101 is intended for subcutaneous injection at an area-adjusted dosage of 2 mg/cm^2, based on a 10 mg/mL concentration of ATX-101 given in 0.2-mL injections, spaced 1-cm apart. The maximum intended dose in a treatment session is 100 mg (ie, 10 mL). ATX-101 may be given in up to 6 treatment sessions, at intervals of not less than 4 weeks. The number of injections in each treatment and the number of treatment sessions are tailored to the individual patient based on the amount and distribution of the patient's SMF and the desired outcome.

Selection of this dosage/injection regimen was based on data from double-blind placebo-controlled Phase 2 studies (Studies 03, 07 and 15), and is further supported by results from Phase 3 studies (Studies 16, 17, 22 and 23). Across these studies, 10 mg/mL ATX-101 was superior to a lower concentration (5 mg/mL) in terms of efficacy as measured by clinician-reported (CR-SMFRS), patient-reported (PR-SMFRS), and objective measures of SMF (MRI, calipers) and its visual/emotional impact (PR-SMFIS), while demonstrating a similar safety profile. Higher local, area-adjusted doses (4 or 8 mg/cm^2), achieved via increased concentration (20 mg/mL) (Study 03), higher volume per injection (0.4 mL) (Study 07), or reduced spacing (0.7 cm; Study 07), did not appear to provide additional efficacy and resulted in a less desirable AE profile (ie, more prolonged or local AEs with increased severity).

2.4. Summary of Nonclinical Development

Although DCA is a well-characterized endogenous substance, Kythera completed a comprehensive panel of nonclinical studies to characterize the toxicity and safety profile of ATX-101, including:

1) In vitro and in vivo pharmacology studies (nonclinical efficacy);
2) Cardiovascular, respiratory and central nervous system safety pharmacology studies;
3) Absorption, distribution and toxicokinetic studies;
4) Single-dose through chronic repeat-dose toxicity, reproductive and genetic toxicology studies;
5) Synthetic DCA and NaDC bridging toxicity studies; drug product formulation bridging toxicity studies; and impurity evaluations.

2.4.1. Pharmacology Studies

2.4.1.1. Primary Pharmacology

Primary pharmacology studies characterized the cytolytic potency and sensitivity of adipose tissue to NaDC. In vitro bridging studies using cultured cells, and an in vivo study in Zucker obese rats were completed to assess drug substance manufacturing changes (animal-derived NaDC to synthetic DCA) and vehicle reformulations.

The median lethal concentration (LC_{50}) of DC was determined in vitro for 7 cultured cell types from distinct lineages; all cell types displayed similar sensitivity to DC. Sodium DC and synthetic DCA formulated in the PBS vehicle showed similar cytolytic effects against cultured MDA-kb2 human breast cancer cells in vitro at concentrations of up to 0.12%. These results are in agreement with literature reports (Gupta et al., 2009).

Pre-incubation with protein-rich tissues significantly reduced DC-induced cell death in A375M melanoma cells compared to pre-incubation with a protein-poor tissue; cytolytic attenuation tracked closely with the relative tissue protein content. Purified collagen and bovine serum albumin also reduced the cytolytic potency of DC on A375M melanoma cells in vitro in a concentration-dependent manner. In vivo, DC concentrations of $\geq$ 0.5% induced cytolysis of adipose tissue in Zucker obese rats whereas concentrations of 0.25% and lower were not effective.

2.4.1.2. Secondary Pharmacology

Lipid released from adipocytes after DCA treatment in rats was shown to be processed by known lipid metabolism pathways. Rats injected with [^{14}C]-triolein (a surrogate marker for lipids) after an injection with 0.5% DCA in PBS showed slow absorption and tissue incorporation of [^{14}C]-triolein-derived radioactivity; tissue distribution was predominantly to fat storage sites, particularly to adipocytes at, and adjacent to, the site of injection. In addition, following a single injection of the emulsified triolein-DCA dose, the majority of the [^{14}C]-triolein-derived radioactivity was metabolized and utilized or excreted within 28 days posttreatment. Two metabolites were detected in urine: suberic acid, a known dicarboxylic acid metabolite of triolein, and an unidentified polar metabolite. Metabolites in plasma and feces were below the detection limit and could not be identified. The results of these secondary pharmacology studies in rats demonstrate that lipids released from adipocytes after DCA treatment were processed in a manner similar to known lipid metabolism pathways (Guyton, 1981).

The area (zone) of cell destruction, based on analysis of cytolysis and apoptosis, following SC injection of 0.5% or 1% ATX-101 was characterized in a pig model. At 48 hours postinjection, tissue samples subjected to terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) analysis showed that the greatest number of TUNEL positive adipocyte nuclei were in the first or second sections (0.5 cm and 1.0 cm) from the point of injection of 1% DCA at 0.2 mL/injection and 0.4 mL/injection, and there were no significant findings at other distances from the injection site. Additionally, TUNEL assessment of the additional 1 mm increment samples (from 1% DCA at 0.2 mL/injection sites) confirmed that no notable DCA effects were observed at a distance greater than 1 cm from the point of injection.

2.4.1.3. Safety Pharmacology

A complete core battery of International Conference on Harmonisation (ICH) compliant safety pharmacology studies was conducted for ATX-101.

Human ether-a-go-go-related gene (hERG) assay: DC concentrations of up to 0.1 μM (0.001%), the lowest in vitro cytotoxic concentration, did not inhibit hERG channel function in transfected Chinese hamster ovary cells.

Cardiovascular/Respiratory: SC ATX-101 doses of ≤ 20 mg/kg did not adversely affect electrocardiographic waveform morphology, QT/QTc intervals, respiratory rate, core body temperature, or blood gases in conscious telemetered Beagle dogs.

Central Nervous System: intravenous ATX-101 doses of ≤ 5 mg/kg did not produce statistically or biologically important differences in neurobehavioral function in rats. Doses of ≥ 5 mg/kg caused reversible local swelling and injection site discoloration. A low incidence of transient and recoverable decreases in motor activity, whole body tremors, hyperpnea and/or loss of righting reflex, ptosis, decreased body temperature, and discolored urine, were observed at 10 mg/kg.

2.4.2. Pharmacokinetics/Toxicokinetics

Nonclinical absorption, distribution, and toxicokinetic (TK) studies of ATX-101 were conducted in animals at pharmacologically and toxicologically relevant doses to support ATX-101 safety in humans. Validated high performance liquid chromatography (HPLC) methods were used for the determination of concentration, stability, and homogeneity in the ATX-101 formulation(s). A validated HPLC tandem mass spectroscopy (HPLC-MS/MS) method was employed for plasma DC measurement. No differentiation of exogenous or endogenous forms was possible as they are structurally and biologically indistinguishable.

2.4.2.1. Absorption

Rats and dogs showed highly variable endogenous DC plasma concentrations (baseline/predose) and food consumption markedly increased circulating DC to maximal concentrations within approximately 2 hours. In comparative SC bioavailability studies, ATX-101 was rapidly absorbed (t_{max} of 0.25 hr and 0.5 hr, in rats and dogs, respectively) and bioavailability was essentially 100% (based on AUC from time 0 to the last quantifiable sample [$AUC_{0\text{-last}}$] values) in both species.

In rats (up to 6-months) and dogs (up to 9-months), C_{max} occurred at ~ 0.25 hour and slightly less than dose-proportional increases in plasma DC concentrations were observed following intermittent SC ATX-101 injection. No apparent DC accumulation or sex difference was observed in either species. Estimates of terminal half-life ($t_{½}$) and related PK parameters for DC were often precluded due to multiple peaks in the concentration-time profiles and insufficient terminal time points due to interference from endogenous DC. No significant differences in concentration-time profiles or PK parameters were observed following SC injection of the final clinical ATX-101 formulation (synthetic DCA in 0.9% BA-PBS) in rats indicating that bioavailability was unaffected by reformulation.

Rabbits showed high basal levels of endogenous DC, which prevented accurate PK characterization of DC however mean C_{max} and $AUC_{0\text{-last}}$ showed no dose-related trend or accumulation at doses of up to 30 mg/kg.

2.4.2.2. Distribution

Subcutaneous [^{3}H]-deoxycholic acid tissue distribution in Sprague-Dawley rats was primarily associated with the small intestine and liver and concentration-time profiles for tissues and plasma indicated some level of tissue retention of [^{3}H]-DCA. Elimination was slow, with a relatively large fraction (13.23%) of administered radioactivity present in tissues and the gastrointestinal contents at 168 hr postdose. These results and the absence of DC accumulation in chronic repeat-dose studies in rats and dogs support exogenous DC recycling.

Plasma protein binding of DC has been reported to be high (98%) in man (Cowen et al., 1975). Endogenous bile acids have been quantified in human fetal serum and milk (Forsyth, 1983; Macias et al., 2009).

2.4.2.3. Metabolism and Excretion

Since the biosynthetic and elimination pathways of endogenous DC in mammals are known, specific metabolism and excretion studies were not conducted for ATX-101 (Angelin et al., 1978; Dawson, 2002; Ekdahl and Sjovall, 1955; Fujii et al., 1988; Hagey et al., 1998; Imamura, 2000; Kasbo et al., 2002; Norman and Shorb, 1962; Street et al., 1983; Stryer, 1995). Endogenous DC is eliminated from the body without further modification and the results of the tissue distribution study suggest that ATX-101 is excreted similarly. Further, PK results indicate an absence of accumulation suggesting that exogenous DC is recycled, reabsorbed from the intestinal tract, and excreted primarily via feces in the same manner as the endogenous molecule.

2.4.2.4. Pharmacokinetic Drug Interaction

Cytochrome P450 (CYP) enzyme inhibition and induction studies suggest that DC has little or no inhibition or induction potential at the intended clinical ATX-101 doses. No direct or time-dependent inhibitory effects were observed on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 by DC in pooled human liver microsomes in vitro. The DC fifty percent inhibitory concentration (IC_{50}) value was greater than 100 µM and the Ki value was estimated to be greater than 50 µM for each of the CYP enzymes evaluated. Further, DC did not exhibit significant potential for in vitro induction of CYP2B6 or CYP3A4 enzymes at concentrations of ≤ 100 µM (1 µM, 10 µM, and 100 µM). These values are more than 10-fold the anticipated clinical C_{max} (approx. 2.6 µM

[1000 ng/mL]) following SC administration of the maximum clinical dose of 100 mg ATX-101 (Study 32).

In vitro efflux and uptake transporter studies also demonstrated that DC has little or no potential for clinically meaningful drug interactions following SC administration at the intended clinical doses (maximum 100 mg/treatment [Study 32]). In efflux-transporter inhibition assays, the IC_{50} values were at least 8-fold greater than the anticipated clinical C_{max} (total) and more than 400-fold greater than the maximum unbound C_{max} concentration. Additionally, the projected IC_{50}/C_{max} (unbound) values for all efflux transporters were greater than 50-fold that of the anticipated clinical C_{max} (unbound) value. In uptake-transporter assays, IC_{50} inhibition values were at least 10-fold higher than the mean DC C_{max} (2.5 µM) for all but OATP1B1, OATP1B3, and sodium-taurocholate cotransporting polypeptide (NTCP) transporters. Calculated R-values were 1.003, 1.002, and 1.023 for OATP1B1, OATP1B3, and NTCP, respectively; these R-values are below the threshold for clinical study requirements (as per the FDA Guidance, 2012) and suggest little potential for clinical interactions with the OATP1B1, OATP1B3, and NTCP transporters. Furthermore, due to extensive serum protein binding of DC, the IC_{50}/C_{max} (unbound) value was projected to be > 300-fold for all uptake transporters except NTCP, which was projected to be 43-fold greater.

2.4.3. Toxicology Program

An ICH compliant toxicology program was completed to support the safety of SC ATX-101 administration for the clinical treatment of SMF. Sprague-Dawley rats and Beagle dogs were the key toxicology species. ATX-101 was injected SC into a single injection site per dose in rats or was approximately equally divided and injected into 4 closely spaced dorsolateral sites in dogs. Due to local injection site effects, dose administrations in repeat-dose studies were rotated between two sites (rats) or sets of injection sites (4 sites/set; dogs) in order to enable a maximum dosing frequency.

2.4.3.1. Single Dose

Single SC ATX-101 doses of ≤ 250 mg/kg (25% DC concentration) in rats and ≤ 100 mg/kg (10% DC concentration) in dogs were systemically well tolerated and local effects were associated with pharmacologically-mediated adipocytolysis (Odo et al., 2007; Thuangtong et al., 2010). A maximum ATX-101 dose of 50 mg/kg was identified for repeat-dose SC administration in both species.

No systemic toxicity, and limited local injection site effects (swelling, necrosis), were observed following single IV ATX-101 administration of ≤ 10 mg/kg in Sprague-Dawley rats and 5 mg/kg in Beagle dogs.

2.4.3.2. Repeat Dose

Subcutaneous ATX-101 administration was well tolerated and no mortality or systemic toxicity was observed following repeated dosing of ≤ 50 mg/kg (≤ 5% in rats; ≤ 10% in dogs) in studies of up to 6 months in rats or 9 months in dogs. Local injection site effects were equivalent between species, were consistent with pharmacologically mediated cytolytic activity, and were reversible.

In all studies, predose plasma endogenous DC levels were highly variable among individual animals fed *ad libitum* and between sexes. Following intermittent-repeat SC ATX-101 administration, DC absorption was rapid (C_{max} at ≥ 0.25 hr postdose), and plasma DC concentrations increased with increasing dose in a slightly less than dose proportional manner up to 50 mg/kg without apparent accumulation or sex difference in either species.

Clinical pathology effects were limited to increases in segmented neutrophils, leukocytes, and/or monocytes in association with local inflammatory reactions to SC ATX-101 dosing. These increases generally reached statistical significance at doses of 50 mg/kg in rats and ≥ 20 mg/kg in dogs and changes were reversible.

The primary in-life, macroscopic, and microscopic findings in all repeat-dose studies in rats and dogs were confined to the injection site and surrounding tissue. In-life dermal signs included pain on injection, a low incidence of erythema and edema, and localized swelling which, at high doses, extended beyond the injection site. Eschar-eschar exfoliation was noted in dogs and ulceration-necrosis was more common in dogs than rats. These changes were reversible over 4- to 6-week recovery periods. Macroscopic observations of injection site discoloration (bruising), skin thickening, and a dose-related severity of subdermal gelatinous material (lysed fat) were consistently noted and were inversely correlated with time postinjection. However, there was no increase in incidence or severity with dosing duration up to 6 months (rats) or 9 months (dogs) and findings were reversed during the post-dosing recovery period.

Histologic injection site findings were similar between species and across studies. In a comprehensive multistudy histopathology review, clinically significant histologic injection site correlates were shown to be consistent across studies and between rats and dogs, and were consistent with local irritative reactions. Effects were generally limited to ATX-101 doses of ≥ 10 mg/kg (concentrations of 1% in rats and 2% in dogs) and findings increased with frequency of injection (Engelhardt, 2008). ATX-101-related injection site lesions followed a temporal progression of acute to subacute inflammation with edema, hemorrhage, and necrosis, to subacute to chronic inflammation with lesser degrees of necrosis and hemorrhage and the presence of fibroplasia and/or fibrosis, to a healing phase of mature fibrosis with minimal to no inflammatory cell infiltration at the end of the 4- to 6-week recovery periods. There was no indication of preneoplastic hyperplasia at or adjacent to the ATX-101 injection sites in any study. Additionally, there were no differences in local injection site reactions between the key toxicology species (rats and dogs) and those observed in local tolerance studies in minipigs.

In the 9-month study in dogs, a glomerular lipid embolus was identified in the kidney of a single male dog given 50 mg/kg (10% concentration; 20 total doses) at the completion of the dosing period. This toxicologically relevant finding was potentially associated with the pharmacologic action of ATX-101 and subsequent inflammatory response. However, following repeated SC ATX-101 dosing at 50 mg/kg, systemic exposure to DC was approximately 3.2-fold higher (AUC_{0-24}) than clinical levels following a 100 mg administration (Study 32), and the duration of exposure (20 intermittent doses over 9 months) was far longer than that intended for the reduction of SMF in humans. No other renal or target organ findings were observed in other repeat-dose studies in dogs or in repeat-dose studies of up to 6 months in rats at the end of dosing or recovery periods.

In 2 separate 28-day bridging studies in Sprague-Dawley rats, there were no toxicological or TK profile differences between groups given 50 mg/kg animal-derived NaDC in sterile water for

injection (SWFI)/0.9% BA vehicle, NaDC in PBS/0.9% BA vehicle, or synthetic DCA in the PBS/0.9% BA vehicle. Additionally, rats given 50 mg/kg NaDC in a PBS-based vehicle, with or without 0.9% BA, had equivalent local dermal reactions, gross observations, and correlating histologic findings. Since no toxicologically important differences were observed between the original ATX-101 drug product (animal-derived NaDC in SWFI/0.9% BA vehicle) and reformulated drug products at the highest tolerated dose level in rats (50 mg/kg), no additional bridging studies were conducted.

2.4.3.3. Genotoxicity

Deoxycholic acid showed no genotoxic potential in a battery of assays conducted in accordance with the ICH S2(R1) guideline; an *in silico* computational assay, an Ames assay, a chromosomal aberration assay in human lymphocytes, and an in vivo rat micronucleus assay.

2.4.3.4. Carcinogenicity

As per agreement with FDA, no long-term carcinogenicity evaluations were conducted. In compliance with relevant guidance, no information arising from nonclinical and clinical studies, or arising from review of the literature, have changed the Sponsor's view on the appropriateness of a carcinogenicity waiver for ATX-101 as currently proposed for acute administration.

No structural alerts were identified in silico and there was no evidence of genotoxicity in the comprehensive battery of in vitro and in vivo genotoxicity studies. Across in vivo SC ATX-101 studies, TK evaluations have demonstrated only transient (< 24 hr) increases in plasma DC above endogenous levels; thus indicating rapid absorption of DC from the injection site without evidence of local retention or accumulation. Further, in chronic toxicity studies in rats and dogs, no local or systemic hyperplasias were identified following repeated SC DC injection at local doses and injection cycle frequencies that exceed what is intended for clinical administration. In humans, ATX-101 will be injected into SC fat tissue; thus, fast-replicating cell types will not be targeted. In addition, the intended clinical treatment regimen for the reduction of SMF is acute in nature. In clinical studies, C_{max} values following SC injection of ATX-101 were within the levels of observed endogenous DC both before and after food consumption (Clinical Studies 08, 24, and 32).

2.4.3.5. Reproductive Toxicity

Reproductive, developmental, and perinatal-postnatal toxicity studies with ATX-101 have been completed in accordance with ICH guidelines (S5[R2], stages A through F of the reproductive process), including dose-ranging studies. ATX-101 was not identified as a developmental toxicant. The overall no observed adverse effect level (NOAEL) for reproductive toxicity was > 50 mg/kg in rats. In rabbits, maternal and fetal NOAELs were < 10 mg/kg and 20 mg/kg, respectively, due to an increase in a common finding of missing intermediate lung lobes in fetuses of dams given 30 mg/kg. This finding was presumed associated with maternal stress and/or local inflammatory effects of SC administered ATX-101.

2.4.3.6. Local Tolerance

Local tolerance studies of up to 2% DC in Göttingen minipigs (1 or 2 SC injections [28-day interval]) showed dermal observations, gross findings, and histopathologic lesions that were

consistent with those observed in rats and dogs. Non-dose-related and nonspecific continual reparative acute-chronic inflammation, fibrosis, or complete resolution was noted over an 8-week observation period.

2.4.3.7. Other Toxicity

In silico computational analyses of DCA-related impurities and synthetic-process intermediates did not identify structural alerts and tested compounds were negative in Ames assays.

2.4.4. Risk Assessment

At the intended clinical administration, the nonclinical pharmacology, PK, and toxicity studies described herein support the safe use of ATX-101 for the improvement in the appearance of convexity or fullness associated with SMF.

Pharmacology evaluations demonstrated the adipocytolytic mechanism of action of DC and the processing of liberated triglycerides and free fatty acids by known fat metabolism pathways. In vitro studies have confirmed DC's differential activity on protein-poor tissues such as adipose tissue compared to protein-rich tissues such as dermis and muscle. Safety pharmacology studies did not identify any cardiovascular, respiratory, or central nervous system adverse effects.

Pharmacokinetic studies showed 100% bioavailability and rapid systemic absorption of DC following SC ATX-101 injection. Tissue distribution and chronic repeat-dose study results demonstrated the absence of DC accumulation and support exogenous DC recycling and reabsorption from the intestinal tract. Although specific studies were not conducted, exogenously administered DC is presumed to exhibit the same metabolism and excretion characteristics as the endogenous molecule since they are biologically indistinguishable. Protein binding is known to be high (approximately 98%) and DC has been quantitated in fetal serum and human milk. In vitro enzyme inhibition and induction studies and efflux and uptake transporter studies suggest that ATX-101 has little or no potential for clinically meaningful drug interactions at the intended clinical doses.

Extensive toxicologic evaluations demonstrated that SC ATX-101 administration is systemically and locally well tolerated at doses, injection frequencies, and durations that significantly exceed the intended clinical administration. Across studies in rats, dogs, and minipigs, most findings were attributed to the pharmacologic action of the drug and ensuing inflammatory reaction. The observations were consistent with effects observed following exposure to an adipocytolytic agent. There were no toxicologic or TK differences between ATX-101 formulated with animal-derived NaDC in BA/SWFI, NaDC in a PBS/BA vehicle, and the intended clinical formulation (synthetic DCA in PBS with BA). ATX-101 (DC) did not demonstrate genotoxic potential and it was not identified as a reproductive toxicant. In addition, potential drug substance and drug product impurities, considered in accordance with regulatory guidelines ICH Q3A(R2), ICH Q3B(R2), and draft ICH M7, raise no concern of unacceptable carcinogenic risk to patients associated with SC administration of ATX-101.

Systemic animal:human exposure multiples at the NOAEL doses in toxicology studies and the quantified clinical exposure from a single-injection PK study in healthy volunteers (Study 32) following treatment with 100 mg (1%) ATX-101, were calculated based on AUC_{0-24} values. Across studies in rats, including the bridging toxicity studies, safety margins ranged from approximately 4 to 6.5-fold; in dogs, the safety margin was 1.7 to 1.9-fold higher. Although the

comparison is made between intermittent-repeat dosing studies in animals and a single-dose PK study in humans, no plasma DC accumulation was demonstrated in nonclinical studies. There are no multiple-dose studies demonstrating PK characteristics in humans.

The local animal:human exposure multiples at the collective (study composite) histopathologic NOAEL doses in rats, dogs, and minipigs and the comparative exposure margins at the maximum local dose (2 mg/site) in man were also calculated. Local exposure multiples of 2.5, 12.5 and 15-fold were determined for rats (6-month), dogs (9-months), and minipigs (local tolerance), respectively. Across species, the spectrum of observed histologic effects at the injection site increased in incidence and severity with dose (concentration) and frequency of injection. ATX-101 dose volume affected only the area of the injection site effects. Based on local NOAELs, clinical administration of up to 1% ATX-101 concentrations (maximum of up to 100 mg) is expected to be well tolerated.

2.4.5. Conclusion from Nonclinical Development Program

Overall, the results of the extensive nonclinical program encompassing pharmacologic, PK, and toxicological evaluations support the safe use of ATX-101 at the intended maximum dosage for improvement in the appearance of convexity or fullness associated with SMF in adults.

2.5. Overview of Clinical Pharmacology

The investigational medicinal product, ATX-101, is a synthetic version of naturally occurring DCA, a well-characterized secondary bile acid found in humans and other mammals that serves to emulsify fats for absorption in the intestine. The homeostasis of bile acids is tightly regulated through several mechanisms, and its biology is well understood and documented. Exogenous DCA, administered as ATX-101, is indistinguishable from endogenous DCA and should be regulated under the same homeostatic mechanisms. ATX-101, containing synthetic deoxycholic acid as its active ingredient, is intended for intermittent administration at a maximum dose of 100 mg per treatment session.

Bile acids, including DCA and bile-acid conjugates, are secreted into the bile ducts and subsequently stored in the gallbladder. Upon food intake, bile acids are secreted into the duodenum to emulsify dietary lipids and cholesterol, which facilitates their absorption. Most (90% to 95%) of the secreted bile acids are reabsorbed and return to the liver through the portal vein via the enterohepatic circulation (Chiang, 2009). Bile acids are rapidly sequestered from the systemic circulation by an efficient hepatic uptake (70% to 90%), resulting in generally low serum levels of bile acids, even after a meal (Angelin et al., 1982). Small quantities (approximately 0.3 to 0.6 g per day) of bile acids are excreted in feces. This small loss is replenished via de novo synthesis of bile acids in the liver and colon. Generally, very little bile acid is excreted in the urine due to highly efficient tubular reabsorption (Steil, 1974; Dawson et al., 2010). The elimination from the systemic circulation and the metabolic fate of DCA upon treatment with ATX-101 are expected to be identical to endogenous DCA.

Baseline endogenous DCA levels in plasma were characterized over a 24-hour period under controlled dietary conditions before the administration of ATX-101 in 4 Phase 1 studies (Studies 08, 18, 24 and 32) conducted in healthy adult patients. High variability of 24-hour baseline DCA levels was observed across the 167 patients evaluated, with values ranging from below the limit of quantitation (BLOQ) (either 50 ng/mL or 25.6 ng/mL) to approximately 1700 ng/mL. These

findings are consistent with the high variation in bile acid levels reported in the literature, especially after food intake (Pennington et al., 1977; Angelin et al., 1982; Setchell et al., 1982). Within an individual, the endogenous DCA levels generally fluctuated across the 24-hour sampling period with no obvious time-associated trend.

Upon SC administration of ATX-101 in humans, DCA levels increased rapidly, reaching maximum plasma concentrations within 1 hour after dosing, which indicates rapid absorption from the injection site. Plasma concentrations of DCA declined thereafter to baseline endogenous levels within 24 hours after dosing. This suggests that DCA is cleared from the systemic circulation rapidly, consistent with observations for naturally-occurring DCA. Due to the fluctuation of endogenous DCA levels, the terminal elimination half-life ($t_{1/2}$) of DCA following SC administration of ATX-101 could not be accurately determined for the majority of patients. Therefore, typical PK parameters such as clearance (CL) and volume of distribution (V) could not be calculated. The C_{max} and AUC_{0-24} (total and baseline-corrected) were used to assess systemic exposure to DCA. The PK observations in human studies are generally consistent with those observed in animal studies, where rapid and complete absorption was observed in both rats and dogs without any indication of depot formation at the site of injection.

Systemic exposure to DCA after ATX-101 administration, measured by C_{max} and AUC_{0-24}, increased with dose across the 24- to 200-mg range tested. However, the increase appeared less than dose proportional at the highest dose evaluated (200 mg). Following ATX-101 SC administration at the maximum intended clinical dose of 100 mg across 5 Phase 1 studies (Studies 08, 18, 24, 30, and 32), the plasma DCA mean C_{max} (range: 733 to 1104 ng/mL) and mean AUC_{0-24} (range: 6650 to 10421 ng.h/mL) were generally 2- to 3-fold higher than baseline endogenous DCA (range: 248 to 441 ng/mL and 3270 to 6045 ng.h/mL, respectively). The impact on plasma DCA levels following the administration of the maximum intended dose (100 mg) of ATX-101 is expected to be minimal since this added amount of exogenous DCA (ie, approximately 3%) is small in comparison to the total bile acids pool of approximately 3 g (Chiang, 2009). It is noteworthy that maximum DCA plasma levels (1600 ng/mL) observed after injection of up to 200 mg ATX-101 (Study 24) into the submental area did not exceed the range of baseline (endogenous) DCA plasma levels observed in the Phase 1 clinical studies (BLOQ to 1700 ng/mL; Studies 08, 18, 24 and 32).

The PK properties of DCA after intermittent repeated treatment sessions have not been investigated. Based on the single-dose results, the small dose administered relative to the bile acids pool (ie, approximately 3%), and the tight homeostasis of bile acids, it is expected that intermittent doses every 4 weeks will not result in accumulation. In a single-dose SMF and abdominal crossover study (Study 30), the predose levels of baseline endogenous DCA were comparable for the 2 study periods separated by a 1-week washout, supporting the conclusion that no accumulation is expected upon repeated 4-week dosing. Lack of systemic accumulation was also demonstrated after twice monthly administration of ATX-101 for up to 6 months in rats and 9 months in dogs (Studies IXB00052 and IXB00076).

A population PK analysis using plasma concentration-time data from a total of 172 patients (79 females and 93 males) in 5 Phase 1 clinical studies in adult patients (Studies 08, 18, 24, 30 and 32) suggested that the 24-hour baseline concentration of DCA tended to increase with age in the range studied (18 to 64 years). However, considering the high interindividual variability observed in endogenous DCA (52%), the small variation in the population estimates (from 107

to 177 ng/mL) in DCA levels is not expected to be of any clinical relevance. The PK of DCA upon ATX-101 administration were adequately described using a 1-compartment model that is parameterized using baseline endogenous DCA concentration, CL, V, and absorption rate constant. The population 24-hour baseline DCA, CL, and V were estimated at 139 ng/mL, 32.5 L/hr, and 193 L, respectively, leading to a calculated $t_{1/2}$ of approximately 4.1 hours. Deoxycholic acid CL and V were independent of dose between 24- and 100-mg with a tendency of approximately 22% lower CL and approximately 76% higher V values at the 200 mg (supratherapeutic) dose. Furthermore, DCA V tended to decrease with higher 24-hour baseline DCA values and to increase with BMI. The population PK analyses did not reveal any significant effect of age, body weight, sex, or race on systemic exposure of DCA at the ranges evaluated in the Phase 1 studies. The increase in V, but not CL, with BMI suggests that obese patients are likely to have lower plasma concentrations compared to non-obese patients. However, lower systemic exposure is of no clinical consequence, as local tolerability and efficacy are not correlated with systemic exposure. None of the covariates identified in the population PK analysis support any ATX-101 dose adjustments.

The choice of the ATX-101 clinical dose (up to 100 mg) was based on efficacy and tolerability/safety results from Phase 2 and 3 clinical studies (Section 3.2). The potential for systemic toxicity due to ATX-101 is mitigated by the following: 1) maximum DCA plasma levels after supratherapeutic (200 mg) doses did not exceed maximum endogenous DCA levels in the population studied, 2) increases in plasma DCA levels are transient (≤ 24 hours), 3) the maximum clinical dose is small (~ 3%) relative to the endogenous pool of bile acids, and 4) the homeostasis of bile acids is tightly regulated. Consistent with this expectation, satisfactory systemic tolerability has been observed in the Phase 2 and 3 clinical studies.

For the same reasons listed above, intrinsic and extrinsic factors known to affect the disposition of other drugs are unlikely to affect the systemic safety or efficacy of ATX-101, the latter being driven by local DCA concentrations at the site of action and not by systemic levels of DCA. Further, since its effect is not related to any receptor binding and activation, genetic and pathophysiological factors are not expected to affect drug response. Therefore, no formal PK/PD analysis of ATX-101 was conducted.

3. REGULATORY HISTORY AND CLINICAL DEVELOPMENT PROGRAM

3.1. Regulatory History

The ATX-101 development program benefited from advice and guidance received from the FDA at numerous time points during development, including a 19 August 2009 Type C Guidance meeting, a 20 April 2011 Type B End-of-Phase 2 meeting, and agreement on key study design elements for the Phase 3 program (FDA letter dated 16 December 2011). In addition, a Type B pre-NDA meeting was held with the FDA on 13 November 2013. All advice received from the Agency was duly considered, and responses were provided and incorporated in the ATX-101 development program as appropriate.

Notable FDA advice that is reflected in the ATX-101 development program includes:

- Development and evaluation of the clinician and patient SMF rating scales (CR-SMFRS and PR-SMFRS) and the SMF impact scale (PR-SMFIS) in accordance with the FDA's PRO Guidance Document (Guidance meeting 19 August 2009)
- Incorporation of objective assessments of SMF reduction through the utilization of MRI measurements in Phase 2 Study 15 (Guidance meeting 19 August 2009) and in subsets of patients enrolled in pivotal Phase 3 Studies 22 and 23, as well as caliper measurements of SMF thickness in pivotal Phase 3 Studies 22 and 23 (End-of-Phase 2 meeting 20 April 2011 and FDA Letter 16 December 2011)
- Use in Phase 3 studies of a primary endpoint consisting of a 2-grade composite SMFRS response and evaluation of the primary endpoint at 12 weeks after the last treatment (FDA Letter 16 December 2011). While Kythera agreed that the 2-grade composite endpoint would provide for a rigorous and robust demonstration of efficacy, based on a substantial body of evidence, Kythera also believed (and continues to believe) that a 1-grade composite SMFRS endpoint better reflects the population of patients who benefit from treatment of their SMF. Therefore, Kythera included the 1-grade composite SMFRS response as a co-primary endpoint in Phase 3 studies, despite the higher hurdle for success that having co-primary endpoints entails.
- Use in Phase 3 studies of a secondary endpoint consisting of the proportion of patients who have at least a 10% reduction from baseline in SMF volume as measured by MRI (FDA Letter 16 December 2011). Kythera also included change from baseline in SMF impact ratings (PR-SMFIS total scale score) as an additional secondary endpoint; the adequacy of the PR-SMFIS as a measure to support secondary labeling claims is being addressed as part of the NDA review.
- Randomized, double-blind, placebo-controlled pivotal Phase 3 study designs with use of the ITT population as the primary analysis population (FDA Letter 16 December 2011)

- Inclusion in the pivotal Phase 3 studies of a LTFU visit at 6 months after last treatment (FDA Letter 16 December 2011)
- Use of the Cochran-Mantel-Haenszel (CMH) test stratified by center, in conjunction with multiple imputation for handling missing data, as the primary method of analysis for the Phase 3 studies (FDA Letter 16 December 2011; FDA letters 06 June 2012 and 20 May 2013)
- Completion of a thorough QT/QTc (TQT) study (Study 24) (Guidance meeting 19 August 2009, FDA letter 21 March 2012)
- Completion of a study that characterizes the PK of the final to-be-marketed formulation using the proposed dosing regimen that is intended for labeling in a suitable number of patients (Study 32) and in vitro metabolic drug-drug interactions study (Study 100000544) (End-of-Phase 2 meeting 20 April 2011 and FDA letter 03 November 2011)
- Agreement that traditional 2-year carcinogenicity assay in rats or mice is probably not necessary to support proposed clinical use (FDA letter 07 May 2009)
- Agreement that the completed nonclinical program appeared to be adequate to support NDA filing (End-of-Phase 2 meeting 20 April 2011 and pre-NDA meeting 13 November 2013)
- Agreement that a full waiver for pediatric studies is appropriate (FDA letter 28 March 2013)

3.2. Clinical Development Program

A comprehensive clinical development program has been undertaken for ATX-101, including Phase 1 safety and pharmacology/pharmacokinetic studies, Phase 1 and 2 preliminary safety and efficacy studies (both for treatment of SMF and for lipomas), Phase 3 confirmatory efficacy and safety studies for treatment of SMF, Phase 3B and LTFU studies, and nontreatment studies that evaluated various efficacy instruments. A listing of all completed and ongoing studies in the ATX-101 clinical program is provided in Table 4.

Table 4: Overview of Completed and Ongoing Clinical Studies in the ATX-101 Development Program

Study No./Status (Indication/Tx Area)	Study Purpose	Design	Total No. of Patients Treated		
			ATX-101	Placebo/ Active Control	Total
Phase 1					
Study 04/Completed (Lipoma)	Safety, efficacy, PK	Multicenter, randomized, double-blind, placebo-controlled, sequential dose escalation, parallel-group	12	4/---	16
Study 08/Completed (SMF)	Safety, PK	Single center, open-label, dose escalation	24	---/---	24
Study 18/Completed (SC abdominal fat)	Safety, serum lipid and adipokine profiles	Single-center, open-label, 2-period	10	---/---	10
Study 30/Completed (SMF & SC abd. fat)	Safety, PK	Single center, open-label, crossover (between SMF and SC abdominal fat)	5	---/---	5
Study 32/Completed (SMF)	Safety, PK, BA and BA-free ATX-101	Single center, open-label	24	---/---	24
Study 24/Completed (SMF)	QT/QTc, PK	Single center, randomized, double-blind, 4-arm, single dose, placebo- and active-controlled	109	54/55 [a]	218
Study 10/Completed (SC abd. fat)	Safety, histologic analysis	Multicenter, open-label	14	---/---	14
Study 19/Completed (SMF)	Safety, comfort, BA vs. BA-free ATX-101	Multicenter, double-blind, within-patient bilateral paired comparison, single dose, safety and comfort	24	---/---	24
Phase 2					
Study 05/Completed (Lipoma)	Safety, efficacy	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	45	17/---	62
Study 03/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	62	22/---	84
Study 07/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	57	14/---	71
Study 15/Completed (SMF)	Safety, efficacy (MRI, PRO measures)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	84	45/---	129
Phase 3					
Study 22/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, 2-arm, placebo-controlled	257 [b]	248/-- [b]	505
Study 23/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, 2-arm, placebo-controlled	258 [c]	256/--- [c]	514
Study 16/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, 3-arm, placebo-controlled	240	122/---	362
Study 17/Completed (SMF)	Safety, efficacy	Multicenter, randomized, double-blind, 3-arm, placebo-controlled	240	114/---	354

Study No./Status (Indication/Tx Area)	Study Purpose	Design	Total No. of Patients Treated		
			ATX-101	Placebo/ Active Control	Total
Phase 3B and Long-term Follow-up					
Study 26/Completed (SMF)	Five month open-label treatment with 1-year long-term follow-up	Multicenter, open-label	165	---/---	165
Study 27/Ongoing (SMF)	Safety, efficacy in patients with baseline CR-SMFRS score of 1 or 4	Multicenter, randomized, double-blind, 3-arm placebo-controlled	60 [d]	30 [d]	90 [d]
Study 28/Ongoing (SMF)	Safety, efficacy in patients aged 65 to 75 years, inclusive	Multicenter, randomized, double-blind, 2-arm, placebo-controlled	30 [d]	30 [d]	60 [d]
Study 36/Completed (SMF)	Safety, management of patient experience	Single-center, randomized, double-blind, 2-factor, placebo-controlled	68	15	83
Study 12/Ongoing (SMF)	Five-year long-term follow-up of safety and durability of efficacy over 9 visits among patients who completed Phase 2 and 3 ATX-101 studies	Nine visits (quarterly, then biannually, then annually)	NA [e]	NA [e]	NA [e]
Study 1403740/Completed (SMF)	Two-year long-term follow-up of safety and durability of efficacy among patients who completed Studies 16 and 17	Three visits (6, 12, and 24 months following last visit in previous study)	NA [f]	NA [f]	NA [f]
Study 35/Ongoing (SMF)	Three-year long-term follow-up of safety durability of efficacy among patients who completed Studies 22 and 23	Three visits (12, 24, and 36 months following last visit in previous study)	NA [g]	NA [g]	NA [g]
Nontreatment Studies					
Study 11/Completed (SMF)	Intra- and inter-rater consistency in CR-SMFRS evaluation	Single-center, one-day	NA	NA	NA
Study 20/Completed (SMF)	Inter- and intra-rater reliability of caliper SMF measurements	Single-center, one-day	NA	NA	NA
Study 21/Completed (SMF)	Comparison of caliper and MRI evaluations of SMF	Single-center	NA	NA	NA
Study 25/Completed (SMF)	Reliability of rating instrument for SMSLG and SMF line drawings	Single-center, one-day	NA	NA	NA

abd = abdominal; BA=benzyl alcohol; CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; MRI = magnetic resonance imaging; NA = not applicable or not available; no. = number; PK = pharmacokinetics; PRO = Patient-Reported Outcomes; SC = subcutaneous; SMF = submental fat; SMSLG = Submental Skin Laxity Grade; Tx = treatment

[a] Moxifloxacin was used as the active control.

[b] The values reflect the inclusion of Patient 124-009 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 4 (Week 8), when ATX-101 was administered in error.

[c] The values reflect the inclusion of Patient 533-006 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 2 (baseline), when ATX-101 was administered in error.

[d] Based on planned enrollment as these studies are ongoing and data remain blinded.

[e] A total of 203 patients previously treated in Phase 2 Studies 03, 07 or 15 were enrolled (65 placebo and 138 ATX-101).

[f] A total of 201 patients previously treated in EU Phase 3 Studies 16 or 17 were enrolled.

[g] A total of 224 patients previously treated in Pivotal Phase 3 Studies 22 or 23 were enrolled.

During the clinical development program for ATX-101, 2664 patients participated in 18 completed treatment studies. Of these 2664 patients, 1698 were treated with ATX-101, 911 were treated with placebo, and 55 were treated with active control.

Across and within the Phase 1, 2, and 3 clinical studies of ATX-101 for reduction of SMF, the dose of ATX-101 (and if applicable, corresponding placebo) was varied in terms of drug concentration, volume of injection, and injection spacing. The dosing regimens used in the Phase 2 and 3 SMF studies that provided dose-selection information as well as pivotal and supportive efficacy and safety data are in Table 5.

Table 5: Summary of ATX-101 Dosing in SMF Efficacy Studies

Study	Study Phase	ATX-101 Concentration[a]	Injection Volume (mL)	Injection Grid (cm)	Maximum Total Volume per Treatment Session (mL)	Max Treatment Sessions	Area-Adjusted Dose (mg/cm^2)
Pivotal US/Canadian Efficacy Studies							
22	3	10 mg/mL	0.2	1	Up to 10	Up to 6	2
23	3	10 mg/mL	0.2	1	Up to 10	Up to 6	2
Supporting Efficacy Studies							
03	1-2	5 mg/mL	0.2	1	Up to 4.8	4	1
		10 mg/mL	0.2	1	Up to 4.8	4	2
		20 mg/mL	0.2	1	Up to 4.8	4	4
07	2	10 mg/mL	0.2	0.7	Up to 9.6	Up to 4	4
		10 mg/mL	0.2	1	Up to 4.8	Up to 4	2
		10 mg/mL	0.4	1	Up to 9.6	Up to 4	4
15	2	5 mg/mL	0.2	1	Up to 10	Up to 6	1
		10 mg/mL	0.2	1	Up to 10	Up to 6	2
16[a]	3	5 mg/mL	0.2	1	Up to 10	Up to 4	1
		10 mg/mL	0.2	1	Up to 10	Up to 4	2
17[a]	3	5 mg/mL	0.2	1	Up to 10	Up to 4	1
		10 mg/mL	0.2	1	Up to 10	Up to 4	2
26[b]	3B	10 mg/mL	0.2	1	Up to 10	Up to 6	2

[a] Study 15 results were not yet available prior to initiation of Studies 16 and 17; therefore, 2 concentrations were included
[b] Single-arm, open-label study
Source: Integrated Summary of Efficacy Table 2 in NDA 206333

3.3. Overview of Efficacy Measures

Reductions in SMF, as reflected by submental convexity or fullness, have been assessed in the pivotal Studies 22 and 23 from the perspective of both the clinician and patient using the clinician rating scale (CR-SMFRS) and patient rating scale (PR-SMFRS), respectively. Assessments of the impact of SMF on patient self-perceptions related to visual and emotional attributes were also collected using the impact scale (PR-SMFIS) as a secondary endpoint. As discussed below, the CR-SMFRS, PR-SMFRS, and PR-SMFIS have been shown to be well-defined and reliable measures capable of evaluating treatment benefit in clinical studies of patients with excess SMF. Patients were also asked other questions related to satisfaction with appearance of their face/chin (SSRS) and to SMF improvement, chin-definition improvement,

and treatment satisfaction (Global Questions regarding improvement and satisfaction). Finally, objective confirmation of SMF reduction was obtained via the use of MRI and caliper measurements. The use of these distinct but related measurement tools captured multiple facets and perspectives associated with SMF reduction. These efficacy measures are described in more detail below, followed by a brief discussion of the development and evaluation of the key clinical outcome assessment instruments developed by Kythera: the CR-SMFRS, PR-SMFRS and PR-SMFIS.

3.3.1. Clinician-reported Submental Fat Rating Scale (CR-SMFRS)

As summarized in Table 6, the CR-SMFRS (clinician rating scale) is a clinician-reported outcome measure that provides a single score rating of SMF size/amount, as reflected by submental convexity or fullness (ie, the extent to which the submental region is bulged, bowed, or rounded outward). Submental convexity, in turn, is largely characterized by the presence and appearance of localized SMF. The clinician rating scale is an ordinal scale that ranges from 0 ("absent submental convexity; no localized SMF evident") to 4 ("extreme submental convexity") in whole-unit increments. To standardize the evaluation, the investigators were provided with a photonumeric guide, showing photographs associated with differing amounts of SMF, and written instructions for use of the clinician rating scale. The rating is based on a live, clinical evaluation of the patient, including: palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; observation of flexion/extension of the neck; and lateral movement of the head. The final score determination is made while the patient's head is in a standardized position. The complete clinician rating scale, with instructions and photonumeric guide, are provided in Appendix A. Detailed training in the use of the clinician rating scale instrument and associated photoguide was provided at investigator meetings; all investigators and subinvestigators who performed CR-SMFRS evaluations received training. Development and evaluation of the performance of the CR-SMFRS is discussed in Section 3.3.6.

Table 6: Clinician-reported Submental Fat Rating Scale (CR-SMFRS)

Score	SMF Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

3.3.2. Patient-reported Submental Fat Rating Scale (PR-SMFRS)

The PR-SMFRS (patient rating scale) is a PRO measure comparable to the clinician rating scale that provides a single ordinal score rating of SMF size/amount, as reflected by submental fullness (Table 7 and Appendix B). In this assessment, patients were asked to look at the area under their chin in a standard, nonmagnifying mirror and answer the question, "How much fat do you have

under your chin right now?" Patients responded using a 5-point descriptive rating scale that ranged from "no chin fat at all" (represented by 0 for analysis purposes) to "a very large amount of chin fat" (represented by 4 for analysis purposes). Study investigators were trained to allow patients to self-administer the patient rating scale (ie, that patients were given a mirror and were to complete the rating on their own, without outside influence), and were instructed to ensure that patient ratings were collected independent of, and without knowledge of, clinician ratings. Development and evaluation of the performance of the patient rating scale is discussed in Section 3.3.6.

Table 7: Patient-reported Submental Fat Rating Scale (PR-SMFRS)

Please look in the mirror at **the area under your chin** to help you answer the following question:

How much fat do you have under your chin right now? Mark ☒ in one box below	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

3.3.3. Patient-reported Submental Fat Impact Scale (PR-SMFIS)

In addition to clinician and patient assessments of relative amounts of SMF as reflected by submental convexity and/or fullness, patients were also asked to rate the visual and emotional impact that the appearance of submental fullness had on their self-perception. Specifically, patients completed the PR-SMFIS (impact scale; Appendix C), an instrument that consists of 6 questions that measure patients' perceptions related to the appearance of their "chin fat" (happy, bothered, self-conscious, embarrassed, looking older, or looking overweight) using an 11-point scale that ranged from 0 (equating to no impact but with wording specifically based on the question) to 10 (equating to extreme impact but with wording specifically based on the question). As with the patient rating scale, the patients were given a mirror along with the impact instrument and were instructed to think about the submental area. Responses to the 6 individual questions were averaged to generate a composite, PR-SMFIS total scale score. For purposes of the composite, scoring for the "happy" question was reversed (reflected) to make it directionally consistent with the other questions. Similar to the clinician and patient rating scales, the impact scale was developed and evaluated according to the FDA's PRO Guidance Document, 2009 and shown to be a well-defined and reliable measure of treatment efficacy. Development and evaluation of the performance of the impact scale is discussed in Section 3.3.6.

3.3.4. Additional Patient-reported Efficacy Measures

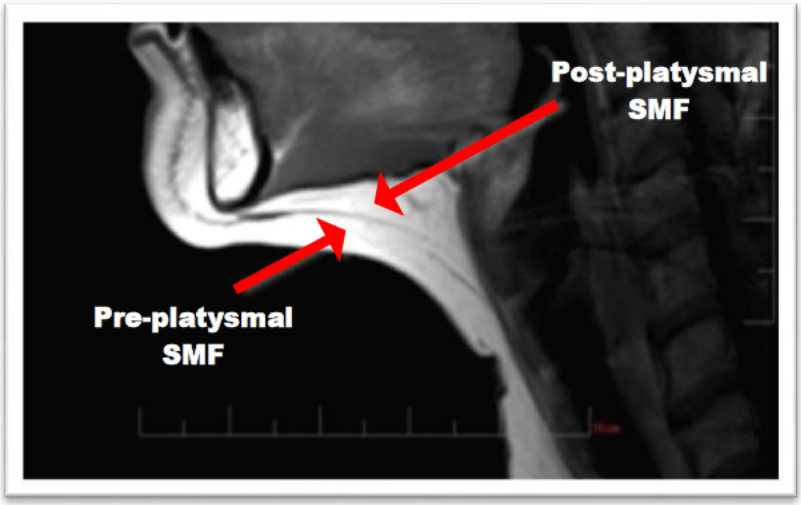
Other patient-reported instruments were also used in the clinical studies to provide supportive information on the efficacy of ATX-101. The SSRS (Appendix D) was a measure that assessed

patient satisfaction with appearance in association with the face and chin using whole numbers on a 7-point scale that ranged from 0 (extremely dissatisfied) to 6 (extremely satisfied). The patients were asked how satisfied they were with their appearance in association with their face and chin without reference to photographs or to previous ratings. Patient-reported SMF line drawings (PR-SMF-LD) were developed based on discussions with the FDA and were used by the patients to assess their submental profile in comparison with a series of 10 line drawings (2 drawings representing each of 5 SMF grades [0 to 4]). Three Global Questions related to improvements in SMF and chin/neck definition, as well as to overall treatment satisfaction (Appendix E) were also used for efficacy assessments as well as to provide clinical anchors for scale interpretability evaluations. Other patient assessments of attractiveness (self-ratings of attractiveness [SRA]) were also used in the pivotal studies, primarily as a means to assess the performance of the other instruments.

3.3.5. Measurement of SMF Using MRI and Calipers

As objective measures of efficacy, the pivotal Phase 3 studies and supportive Phase 2 Study 15 included MRI assessments to determine pretreatment and posttreatment SMF volume and thickness within a defined region. Standardized procedures were used to obtain MRI measurements, including precise patient positioning, and relevant training of investigational center personnel was provided. A blinded central evaluator read all of the MRIs. Figure 3 shows a sample MRI image that indicates the preplatysmal SMF, which is intended to be treated with ATX-101, as well as the postplatysmal SMF, which is not treated. While the platysma is clearly visible in this image, only a fraction of MRI images reveal this demarcation. Therefore, the entire depth of SMF was measured to allow for standardized and reproducible MRI evaluations, although only a portion of the fat is subject to reduction via ATX-101. SMF volume was measured by acquiring contiguous MRI slices (10 mm thickness) in the sagittal plane across the entire submental region. The cross-sectional area of SMF at the mid-sagittal plane was then measured and multiplied by the slice thickness to determine the volume of SMF for endpoint/analysis purposes. A single mid-sagittal slice was used because: 1) there is no clearly defined lateral boundary of the SMF compartment; and 2) it provided the clearest depiction and most reproducible measurement of the SMF (off-axis slices demonstrated blurred borders with the surrounding tissue and air, which compromised the precision of the SMF measurement).

Figure 3: Sample MRI Image of Submental Fat



In pivotal Studies 22 and 23, a 10% reduction in MRI volume was used to define a responder. This criterion was conservatively set based on data from Phase 2 Study 15 and in discussion with the FDA. Using anchor-based analyses similar to those discussed in Section 3.3.6, a 10% reduction in MRI volume discriminated between patients who reported little-to-no global improvement in their SMF and those who reported higher levels of improvement in SMF. In Study 15, a mean reduction in MRI volume of 7.1% was associated with patients reporting that their SMF was at least "moderately better" according to a global improvement question. In the interest of providing robust assurance that treatment with ATX-101 was resulting in clinically meaningful and interpretable reductions in SMF volume, and in consultation and agreement with the FDA, Kythera adopted a 10% change in SMF volume as the threshold for MRI response; this volume change is more closely associated with patients who reported that their SMF was "a great deal better" posttreatment.

External caliper measurements were also used to objectively determine the thickness of SC fat tissue in the submental area. With thumb and fingers about 2 to 3 inches apart, the investigator grasped the submental fat, pulled it way from the bottom of the chin and placed the caliper tips on the SMF skinfold, just above the thumb/forefinger and halfway between the submental crease and the base of the fold (near the body/neck). Precision mechanical body fat calipers with a visual pressure indicator were used to allow for precise readings when the user achieved the correct pressure on the submental fat pad being measured, and measurements were repeated until 2 identical values were obtained.

While objective confirmation of SMF reduction was requested by the FDA (specifically, MRI) and was considered critically important, such measures were not used as primary efficacy endpoints because clinical benefit for aesthetic treatments is best determined by, and should be readily apparent to, the patient and the clinician.

3.3.6. Development and Evaluation of Clinical Outcome Assessment Instruments for SMF

The rationale for developing the CR-SMFRS, PR-SMFRS, and PR-SMFIS was to have well-defined, valid, and reliable tools to measure ATX-101 treatment effects in the SMF clinical development program. The CR-SMFRS, PR-SMFRS, and PR-SMFIS were developed and evaluated in a manner consistent with recommendations from the FDA's PRO Guidance Document, 2009 and industry best practices, including the analytical approaches employed to evaluate and confirm the psychometric performance (ie, measurement properties) and interpretability of each measurement.

Evidence from the literature and concept elicitation interviews with clinicians and individuals with excess SMF indicated that amount/size of SMF, as reflected by submental convexity/fullness, is the most important attribute of SMF and a relevant target for SMF reduction treatment. These sources also suggested that the negative impacts of SMF on patients' perceptions of looking older and overweight (ie, visual impact) and feeling unhappy, bothered, self-conscious, and embarrassed (ie, emotional impact) by the appearance of submental fullness (ie, SMF amount/size) are relevant SMF measurement concepts. After establishing the importance and relevance of the measurement concepts, reviewing the literature for appropriate measures of psychosocial status as associated with facial aesthetic procedures and consulting with experts in the field, Kythera determined that no existing instrument was suitable for the ATX-101 program and therefore undertook development of new instruments that address these concepts. The CR-SMFRS, PR-SMFRS and PR-SMFIS were developed based on expert and patient input and each of these instruments were then evaluated via a panel of clinicians (CR-SMFRS) and via debriefing interviews with patients interested in SMF treatments (PR-SMFRS and PR-SMFIS). Results from these interviews, in concert with results from the aforementioned concept elicitation interviews, support the content validity of the instruments; ie, they measure concepts that are relevant to SMF and important to individuals seeking SMF reduction treatment, and they do so in ways that respondents understand and to which they can provide meaningful responses.

Using data from the CR-SMFRS reliability study (Study 11; N = 66) and a Phase 2 dose-ranging study (Study 15; N=129), the psychometric performance of scores produced by the CR-SMFRS, PR-SMRFS, and PR-SMFIS were evaluated and documented prior to the conduct of pivotal Phase 3 studies. These evaluations indicated that the 6 items in the PR-SMFIS were related but independent and that the CR-SMFRS, PR-SMFRS, and PR-SMFIS produced scores that were: (1) reliable based on internal consistency and test-retest evaluations within and between raters, (2) construct-valid based on correlations to related concepts/measures, and (3) sensitive to change over time. The results confirmed that the instruments were suitable for use in evaluating efficacy hypotheses in ATX-101 pivotal studies. Following completion of the Phase 3 program, the psychometric performance of the target instruments was reevaluated based on data from 5 Phase 3 trials, including the 2 pivotal Phase 3 studies conducted in the US and Canada (Study 22; N = 506, and Study 23; N = 516), 2 supportive EU Phase 3 studies (Study 16; N = 363, and Study 17; N = 358), and open-label Phase 3B Study 26 (N = 165). Consistent results were obtained from the Phase 2 and Phase 3 evaluations, confirming that the CR-SMFRS, PR-SMFRS, and PR-SMFIS produce scores that are reliable and construct-valid, capable of distinguishing between groups known to be different, and sensitive to change over time. As

such, the 3 instruments were confirmed to be suitable to evaluate efficacy hypotheses associated with the reduction of SMF.

Interpretation of changes in scores for the CR-SMFRS, PR-SMFRS and PR-SMFIS was evaluated primarily using anchor-based methods, with distribution-based methods and cumulative distribution functions serving as secondary analyses. The primary clinical anchor was a patient global impression of change (PGIC) item that prospectively targeted "moderately better" SMF as being indicative of clinically meaningful improvement. On this basis, the anchor-based assessments conducted using both Phase 2 and Phase 3 data indicated that 1-grade reductions in ratings on the CR-SMFRS and PR-SMFRS represent clinically meaningful improvements based on their association with patient global assessments of moderate improvement. These results were further corroborated by comparable results when using an anchor based on moderate patient satisfaction with treatment. Similar analyses among patients who reported moderate global improvement on the PGIC indicated that, across the Phase 2 and Phase 3 studies, approximately 3-point improvements on the PR-SMFIS represent clinically meaningful changes.

The 2 primary endpoints used in ATX-101 pivotal Phase 3 Studies 22 and 23 were:

- 1-grade composite SMFRS response rate at 12 weeks after last treatment (ie, proportions of patients who simultaneously demonstrate at least 1-grade improvement on both the clinician rating scale (CR-SMFRS) and the patient rating scale (PR-SMFRS); and
- 2-grade composite SMFRS response rate at 12 weeks after last treatment (ie, proportions of patients who simultaneously demonstrate at least 2-grade improvement on both the clinician and patient rating scales).

As an exploratory analysis, the ability of each of these composite endpoints to correctly identify patients who did or did not indicate that their SMF was at least moderately better following treatment was assessed using 2 x 2 contingency tables comparing responder status (yes/no) vs. several self-reported assessments of treatment benefit, including PGIC and satisfaction measures (each categorized into improved/not improved). For example, among patients who met the 1-grade composite SMFRS endpoint in pivotal Studies 22 and 23, the large majority assessed their SMF as being at least moderately better posttreatment by PGIC (77% to 81% of patients), were at least moderately satisfied with treatment (82% to 84% of patients per the global satisfaction question) and were at least slightly satisfied with their appearance in relation to their face and chin (85% to 88% of patients per the SSRS). While the 2-grade composite definition also identified a population with a high degree of meaningful improvement, using such a stringent definition for success excluded a large proportion of the patients who perceived a treatment benefit. For example, of 414 patients in the pivotal studies who reported at least moderately better SMF posttreatment, only 82 (19.8%) were 2-grade composite SMFRS responders, whereas 344 (83.1%) were 1-grade composite SMFRS responders. Thus, having both the 1-grade and 2-grade composite SMFRS primary endpoints allowed for an evaluation of the effects of ATX-101 at 2 different levels with differing utilities. One (2-grade composite) provides a robust demonstration of efficacy by identifying patients with a very high degree of benefit while the other (1-grade composite) more accurately reflects the patients who experienced clinically meaningful improvement.

Together the development and evaluation information indicate that the CR-SMFRS, PR-SMFRS, and PR-SMFIS are fit for the purpose of supporting ATX-101 product labeling. The instruments have direct links to ATX-101 efficacy hypotheses and demonstrate good content validity (ie, the instruments measure concepts that are relevant to SMF and important to patients interested in real-world SMF treatments, and do so in ways in which respondents can understand and to which they can provide meaningful responses), psychometric performance (ie, the instruments generate scores that are reliable, valid, and sensitive to change), and interpretability (ie, identified changes in scores can be clearly distinguished as meaningful from the perspective of the patient seeking treatment). Regarding the latter, 1-grade improvements on the CR-SMFRS and PR-SMFRS can be considered to be clinically meaningful based on their association with at least moderate global improvement and a high level of patient satisfaction, both with treatment and with their appearance in relation to their face and chin. Approximately 3-point improvements in the PR-SMFIS total scale score can similarly be interpreted as indicative of patient benefit.

4. EFFICACY IN PIVOTAL PHASE 3 STUDIES AND IN SUPPORTIVE AND LONG-TERM FOLLOW-UP STUDIES

4.1. Selection of ATX-101 Dosing Regimen Used in Pivotal Studies

Pivotal Studies 22 and 23 evaluated a 2 mg/cm^2 dose of ATX-101, which was delivered at a concentration of 10 mg/mL, in 0.2-mL injections spaced 1 cm apart (using a 1-cm grid). The number of injections in each treatment session and the number of treatment sessions were tailored to the individual patient based on the amount and distribution of their SMF. A maximum of 10 mL (100 mg DCA) was administered per treatment in up to 6 treatment sessions at intervals of not less than 4 weeks apart.

The 2 mg/cm^2 dosing regimen was selected based on efficacy and safety data from Phase 2 SMF Studies 03, 07 and 15 and is further supported by results from EU Phase 3 Studies 16 and 17. As described in Table 5 in Section 3.2, these studies evaluated a range of ATX-101 concentrations (5 to 20 mg/mL), injection spacings (0.7 or 1 cm grids), volumes per injection (0.2 or 0.4 mL), and maximum number of treatments (4 or 6). Among several endpoints, the 1-grade CR-SMFRS response was a key outcome common to all studies and results for this endpoint based on observed data at a common timepoint (ie, 12 weeks after last treatment) are provided in the tables below, with shading to indicate the recommended dose used in pivotal studies. Based on these and other data, Kythera concluded:

- From Study 03 (Table 8), that a 5 or 10 mg/mL concentration of DCA was likely to be effective; higher concentrations (20 mg/mL) did not appear to be warranted.

Table 8: Study 03 (Concentration) Dose-ranging – 1-grade CR-SMFRS Response

Placebo (0.2 mL/inj., 1 cm grid)	**ATX-101 1 mg/cm^2** (5 mg/mL, 0.2 mL/inj., 1 cm grid)	**ATX-101 2 mg/cm^2** (10 mg/mL, 0.2 mL/inj., 1 cm grid)	**ATX-101 4 mg/cm^2** (20 mg/mL, 0.2 mL/inj., 1 cm grid)
22.7% (5/22)	60.0% (12/20)	75.0% (15/20)	63.6% (14/22)

Source: Integrated Summary of Efficacy Table 25 in NDA 206333

- From Study 07 (Table 9), which included a fixed 10 mg/mL concentration of ATX-101, that increasing local doses by increasing volume per injection (to 0.4 mL) or reducing spacing between injections (to 0.7 cm) may slightly improve efficacy, but this was countered by more severe/prolonged AEs.

Table 9: Study 07 (Injection Volume/Spacing) Dose-ranging – 1-grade CR-SMFRS Response

Placebo (All dosing regimens)	ATX-101 2 mg/cm^2 (10 mg/mL, 0.2 mL/inj., 1 cm grid)	ATX-101 4 mg/cm^2 (10 mg/mL, 0.4 mL/inj., 1 cm grid)	ATX-101 4 mg/cm^2 (10 mg/mL, 0.2 mL/inj., 0.7 cm grid)
35.7% (5/14)	69.2% (9/13)	75.0% (15/20)	79.2% (19/24)

Source: Integrated Summary of Efficacy Table 25 in NDA 206333

- From Study 15 (Table 10), that a 10 mg/mL concentration appeared to be more effective than 5 mg/mL by clinician, patient and objective measures (without a difference in safety profile) and was more likely to produce results that would support approval of ATX-101 in the US. EU Phase 3 Studies 16 and 17 were initiated prior to knowing results of Study 15 and therefore also included both the 5 and 10 mg/mL concentrations. Results from those studies also support the 10 mg/mL concentration that was selected for use in pivotal Studies 22 and 23 (additional data from the EU Phase 3 studies are provided in Section 4.3).

Table 10: Phase 2-3 (Concentration) Dose-ranging – 1-grade CR-SMFRS Response

Study	Placebo (All dosing regimens)	ATX-101 1 mg/cm^2 (5 mg/mL, 0.2 mL/inj., 1 cm grid)	ATX-101 2 mg/cm^2 (10 mg/mL, 0.2 mL/inj., 1 cm grid)
15	31.1% (14/45)	55.0% (22/40)	61.9% (26/42)
16	23.0% (28/122)	57.5% (69/120)	64.5% (78/121)
17	32.8% (38/116)	56.7% (68/120)	61.5% (75/122)

Source: Integrated Summary of Efficacy Table 25 in NDA 206333

4.2. Pivotal Efficacy Studies 22 and 23

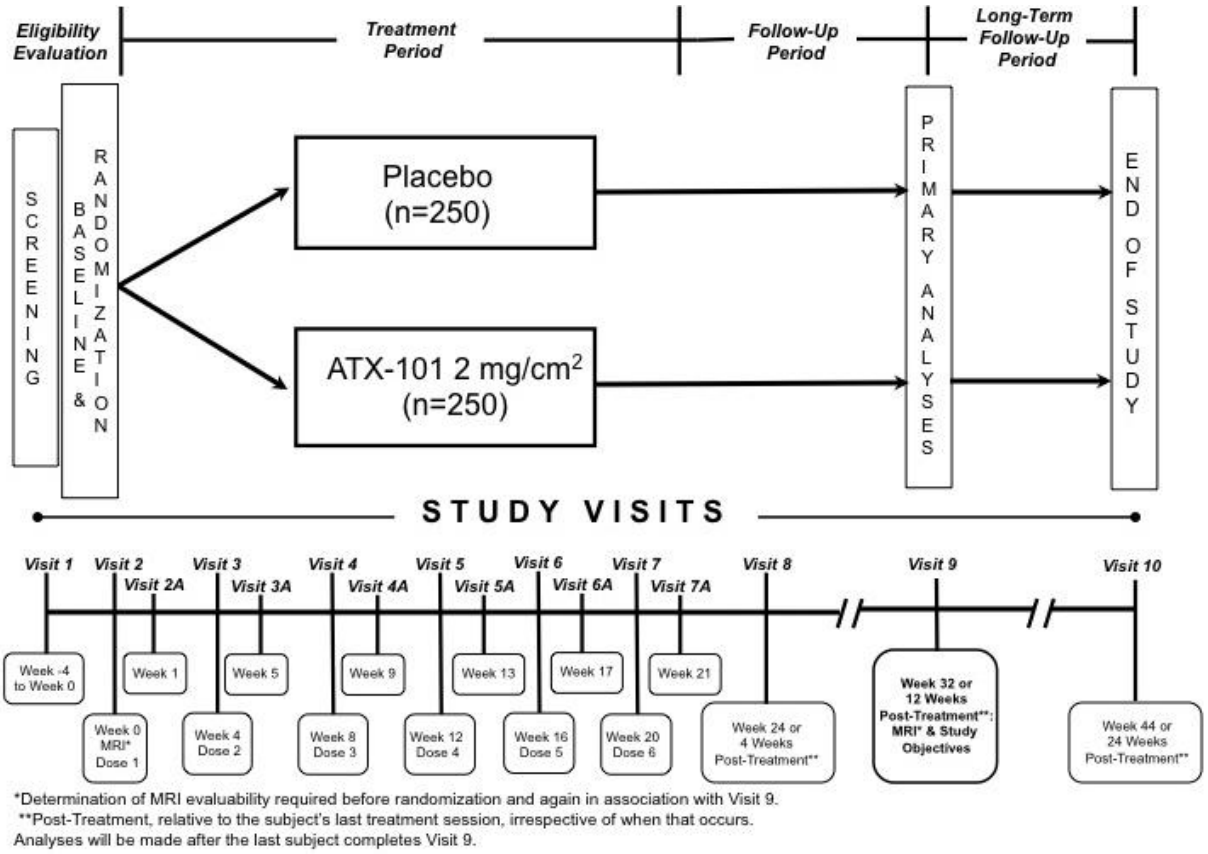
4.2.1. Study Design

Pivotal Studies 22 and 23 were multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies of ATX-101 for the reduction of localized SC fat in the submental area. Both studies were conducted using identical study protocols, including identical inclusion/exclusion criteria, study designs, endpoints and planned statistical analyses. The studies were conducted simultaneously at 70 investigational centers in the US and Canada. There were 35 unique sites per study; no investigational center participated in both studies.

Over 500 patients were enrolled in each of these studies and were randomized to receive either ATX-101 or placebo in a 1:1 ratio. Placebo consisted of vehicle, including BA preservative, with the salt content increased slightly to provide comparable tonicity. Study drug was administered in multiple 0.2 mL injections spaced 1-cm apart, resulting in an area-adjusted

ATX-101 dose of 2 mg/cm^2 (based on the 10 mg/mL concentration of DCA in ATX-101). Patients could receive up to 10 mL of study drug per treatment session and up to 6 treatment sessions at 28-day (± 5 days) intervals. The number of injections in each session was determined by the investigator based on the amount and distribution of SMF. Patients returned approximately 1 week after each treatment for safety evaluation. Follow-up visits were scheduled at 4 weeks (Visit 8), 12 weeks (Visit 9), and 24 weeks (Visit 10) weeks after the last treatment for each patient. A schematic diagram of the study design is presented in Figure 4.

Figure 4: Study Design Schematic for Pivotal Phase 3 Studies 22 and 23



The objectives and related endpoints of these studies were to evaluate the efficacy of 2 mg/cm^2 ATX-101 SC injections in the submental area, relative to placebo, for the following:

Primary:

The co-primary efficacy endpoints were:

- the 1-grade composite SMFRS response rate at 12 weeks after last treatment (Visit 9) (ie, the proportion of patients who simultaneously have at least a 1-grade improvement on the clinician rating scale [CR-SMFRS] and at least a 1-grade improvement on the patient rating scale [PR-SMFRS])
- the 2-grade composite SMFRS response rate at 12 weeks after last treatment (Visit 9) (ie, the proportion of patients who simultaneously have at least a 2-grade improvement on the CR-SMFRS and at least a 2-grade improvement on the PR-SMFRS)

Secondary:

- The reduction in SMF volume measured using MRI, as assessed by the proportion of patients who had at least a 10% volume reduction at 12 weeks after last treatment (based on a subset of at least 200 patients in each study undergoing MRI evaluations at selected centers in each study). During enrollment of the MRI subset, all patients enrolled at the selected centers underwent MRI evaluations. Imaging was conducted during the screening period and again in association with Visit 9 (12 weeks, ±1 week, after the patient's last treatment session). All MRIs were evaluated for acceptability and were repeated as necessary.
- Improvement in the self-perceived visual and emotional impacts of SMF as assessed by mean changes from baseline to 12 weeks after last treatment in the PR-SMFIS total scale score.

Additional:

Improvement in other measures of SMF, including:

- Measurements of thickness of SMF using calipers, patient satisfaction with the appearance of their face/chin based on the SSRS, changes in PR-SMF-LD ratings, and Global Questions regarding improvement in SMF, improvement in chin/neck definition, and treatment satisfaction.
- Changes in CR-SMFRS, PR-SMFRS, PR-SMFIS, and other measures at alternate timepoints during the study.

Several design elements were included in the pivotal studies in order to implement blinded trials. The placebo consisted of inactive vehicle, including BA preservative (with the salt content increased slightly to provide comparable tonicity), and was indistinguishable from the active drug in both external appearance and physical injection characteristics. With the exception of a unique kit code, placebo and active drug were identically labeled prior to shipment to the investigational sites. Patients were then randomized and assigned a kit code via a web-based system. With respect to trial conduct, clinician and patient ratings of SMF were collected independent of each other and without knowledge of ratings at previous time points. Additionally, two objective measures (MRI and caliper assessments) were included in the studies. In particular, the MRI assessments were evaluated by a central blinded reviewer who had no access to any other patient records, assuring that this measure was not subject to perceptual bias.

4.2.2. Key Enrollment Criteria

Within the clinical efficacy studies, a patient population appropriate for evaluation of ATX-101 was included. In particular, within the pivotal Phase 3 Studies 22 and 23, the enrollment included:

- Male and female patients 18 to 65 years of age, with stable body weight, and BMI of ≤ 40 kg/m^2

- Patients with SMF rated by the investigator as 2 or 3 (ie, moderate or severe) on the CR-SMFRS, rated by the patient as 2 or 3 on the PR-SMFRS, and considered undesirable by the patient as characterized by a score of 0, 1, or 2 on the SSRS
- Patients with no prior intervention for SMF (eg, liposuction, surgery, or lipolytic agents), and without excessive skin laxity
- Patients without evidence of any cause of enlargement of the submental area other than SMF (eg, thyroid enlargement or cervical adenopathy) and without a history of trauma associated with the chin/neck that may affect evaluation of safety or efficacy
- Patients with stable body weight (in the judgment of the investigator) for at least 6 months and agreeing to refrain from making significant changes in dietary or exercise habits during the study
- Patients medically able to undergo the administration of study material (based on clinical and laboratory tests) and with no medical condition that would interfere with assessment of safety or efficacy or compromise the patient's ability to undergo study procedures or give informed consent

4.2.3. Statistical Analysis

Sample size power calculations were performed for the co-primary and secondary endpoints. Estimates of treatment effects (eg, response rates) were obtained from an earlier Phase 2 study (Study 15). The planned study sample size of 250 patients per treatment arm in each study provided > 99% power to detect a difference in the 1-grade composite SMFRS (CR and PR) endpoint of 57.1% vs. 22.2% and 93% power to detect a difference in the 2-grade composite endpoint of 9.5% vs. 2.2%. As these two primary endpoints were treated as co-primary, the resulting statistical power to meet the primary endpoint analysis was 93%. This sample size also provided > 99% power to detect a difference in the mean change from baseline in the PR-SMFIS total scale score of -4.27 vs. -2.21 (assuming standard deviations of 2.48 and 2.34 respectively). The proposed sample size of 100 per treatment arm in the MRI subset provided > 99% power to detect a difference in MRI responder rate of 48.7% vs. 7.1%.

All study endpoints were summarized using descriptive statistics appropriate to the scale of measurement. Formal hypotheses tests were conducted for the primary and secondary endpoints using the ITT population (defined as all randomized patients, analyzed according to their assigned treatment group). The ITT-MRI population (ie, the subset of randomized patients who were enrolled to undergo MRI assessment) was used for the MRI endpoint. For all primary analyses, missing data was imputed using a multiple imputation model that included demographic and baseline characteristics, treatment group, and relevant patient data from earlier timepoints. The co-primary endpoint analyses of 1-grade composite SMFRS responders and 2-grade composite SMFRS responders were tested using the CMH general association test statistic, stratified on investigational center. Sensitivity analyses were performed with missing data imputed using last observation carried forward (LOCF), using observed cases only, and also using alternate statistical tests (eg, logistic regression). No adjustment for multiplicity was applied to the analysis of the co-primary efficacy endpoints since both endpoints were required to be met for the studies to be considered successful. Change from baseline data were analyzed as continuous variables using an analysis of covariance (ANCOVA) with treatment and the

appropriate covariate (ie, the baseline value for the variable of interest) included in the model. Analysis of the secondary endpoints was only to be performed if the primary endpoints were met; to address multiplicity, a Bonferroni-Holm procedure was used in the testing of the 2 secondary efficacy endpoints of MRI responder and PR-SMFIS total scale score change from baseline. The safety population was used for all summaries of safety endpoints, based on patients' actual treatments received. Incidence, severity, and duration of AEs were tabulated by treatment group; descriptive statistics were used to characterize changes from baseline in laboratory test results, vital signs, and weight.

4.2.4. Study Populations

4.2.4.1. Demographics

The demographic and baseline characteristics of the 1022 patients included in the pivotal Phase 3 studies (N = 506 in Study 22; N = 516 in Study 23) were similar across the individual studies and between treatment groups within each study. Further, the demographic and baseline characteristics of patients randomized to treatment in both studies are consistent with those of patients in the general population who would be expected to use ATX-101 in the commercial setting. Detailed treatment group demographics for each study and for the pooled pivotal studies are presented in Table 11. In both studies, the ATX-101 and placebo treatment groups were well balanced; most patients were female (83.2% to 86.8%), white (85.2% to 90.8%) and not Hispanic/Latino (84.5% to 93.2%), with a mean age of 47.6 to 49.5 years, and a mean BMI of approximately 29 kg/m^2. The patients were evenly split between moderate (grade 2) and severe (grade 3) SMF as rated by the clinician using the CR-SMFRS.

Table 11: Summary of Demographic and Baseline Characteristics in Pivotal Studies 22 and 23

	Study 22		Study 23	
Characteristics	**Placebo N = 250**	**ATX-101 2 mg/cm^2 N = 256**	**Placebo N = 258**	**ATX-101 2 mg/cm^2 N = 258**
Sex, n (%)				
Male	42 (16.8)	43 (16.8)	34 (13.2)	37 (14.3)
Female	208 (83.2)	213 (83.2)	224 (86.8)	221 (85.7)
Age (years)				
n	250	256	258	258
Mean (SD)	49.4 (9.33)	49.5 (9.30)	47.6 (8.99)	48.2 (9.30)
Race, n (%)				
White	227 (90.8)	218 (85.2)	222 (86.0)	222 (86.0)
Black or African American	13 (5.2)	24 (9.4)	21 (8.1)	24 (9.3)
Asian	5 (2.0)	7 (2.7)	5 (1.9)	4 (1.6)
American Indian or Alaska Native	2 (0.8)	0	2 (0.8)	1 (0.4)
Native Hawaiian or Pacific Islander	1 (0.4)	0	1 (0.4)	3 (1.2)
Multiple	0	2 (0.8)	0	2 (0.8)
Other	2 (0.8)	5 (2.0)	7 (2.7)	2 (0.8)
Ethnicity, n (%)				
Hispanic/Latino	17 (6.8)	28 (10.9)	39 (15.1)	40 (15.5)
Not Hispanic/Latino	233 (93.2)	228 (89.1)	219 (84.9)	218 (84.5)
Weight (kg), n	249	256	257	257
Mean (SD)	80.98 (14.296)	81.15 (14.549)	80.31 (15.041)	81.38 (14.791)
BMI (kg/m^2), n	249	256	257	257
Mean (SD)	29.26 (4.281)	29.23 (4.406)	29.30 (4.282)	29.22 (4.755)

	Study 22		Study 23	
Characteristics	**Placebo N = 250**	**ATX-101 2 mg/cm^2 N = 256**	**Placebo N = 258**	**ATX-101 2 mg/cm^2 N = 258**
CR-SMFRS rating, n (%)				
2	130 (52.0)	130 (50.8)	131 (50.8)	126 (48.8)
3	119 (47.6)	126 (49.2)	126 (48.8)	131 (50.8)
Missing [a]	1 (0.4)	0	1 (0.4)	1 (0.4)
PR-SMFRS rating, n (%)				
2	156 (62.4)	164 (64.1)	160 (62.0)	162 (62.8)
3 [b]	93 (37.2)	92 (35.9)	97 (37.6)	95 (36.8)
Missing [a]	1 (0.4)	0	1 (0.4)	1 (0.4)
Fitzpatrick skin type, n (%)				
I: light, pale white	14 (5.6)	11 (4.3)	18 (7.0)	23 (8.9)
II: white, fair	73 (29.2)	89 (34.8)	69 (26.7)	63 (24.4)
III: medium, white to olive	100 (40.0)	80 (31.3)	89 (34.5)	84 (32.6)
IV: olive, medium brown	43 (17.2)	53 (20.7)	57 (22.1)	56 (21.7)
V: brown, dark brown	15 (6.0)	18 (7.0)	19 (7.4)	23 (8.9)
VI: black, very dark brown to black	5 (2.0)	5 (2.0)	6 (2.3)	9 (3.5)
SMSLG Score, n (%)				
None/Mild	207 (82.8)	217 (84.8)	214 (82.9)	213 (82.6)
Moderate/Severe	42 (16.8)	39 (15.2)	43 (16.7)	44 (17.1)
Missing	1 (0.4)	0	1 (0.4)	1 (0.4)

BMI = body mass index; CR = clinician-reported; ITT = intent-to-treat; PR = patient-reported; SD = standard deviation; SMFRS = Submental Fat Rating Scale; SMSLG = Submental Skin Laxity Grade

[a] Missing baseline values for CR-SMFRS and PR-SMFRS were imputed as part of the multiple imputation procedure.

[b] Includes 1 placebo patient in Study 22 with a baseline PR-SMFRS rating of 4.

Notes: Percentages are based on the number of ITT patients (N) in a given treatment group. Race category of "Other" includes patients reporting race as "Other" and patients reporting more than 1 race.

Source: Integrated Summary of Efficacy Posttext Table 2.1 in NDA 206333

4.2.4.2. Patient Disposition

Patient dispositions in Studies 22 and 23 are summarized in Table 12. In both studies, a similar percentage of patients in each treatment group completed the studies through the final follow-up visit (Visit 10) at 24 weeks after last treatment (82.9% to 88.3% for ATX-101 and 86.8% to 90.8% for placebo). The most common reasons for study discontinuation were patient convenience and loss to follow-up. A slightly higher proportion of patients were evaluated at Visit 9 at 12 weeks after last treatment, the primary efficacy timepoint (85.7% to 91.0% for ATX-101 and 89.1% to 93.2% for placebo), indicating that there was an acceptably low level of missing data for the key efficacy evaluations.

In both studies, a lower percentage of patients in the ATX-101 group than in the placebo group completed the maximum number of 6 treatments (53.9% to 64.1% for ATX-101 versus 77.1% to 85.2% for placebo). For the total of 211 patients in the ATX-101 group who received fewer than 6 treatment sessions across both studies, 2 of the most common reasons were related to efficacy of treatment, or therapeutic success. For 77 of the 211 patients (36.5%), the reason was insufficient remaining SMF and for 21 of the 211 patients (10.0%), the reason was patient satisfaction with SMF reduction. Other common reasons included AEs (36 ATX-101 patients; 6 placebo patients), withdrawal of consent for further treatments due to patient convenience (27 ATX-101 patients; 22 placebo patients) and loss to follow up (16 ATX-101 patients; 10 placebo patients). Regarding the "Other" category for completing fewer than the maximum number of treatment sessions, which is skewed toward patients treated with placebo (4 ATX-101 patients and 28 placebo patients across both studies), for all but one of these patients the reason was cited as dissatisfaction with treatment results.

Table 12: Patient Dispositions in Pivotal Studies 22 and 23

	Study 22		Study 23	
	Placebo N = 250 n (%)	**ATX-101 2 mg/cm^2 N = 256 n (%)**	**Placebo N = 258 n (%)**	**ATX-101 2 mg/cm^2 N = 258 n (%)**
Randomized Patients (ITT Population)	250	256	258	258
Patients in the ITT-MRI Population	111	113	112	113
Study Completion				
Received 6 treatments	213 (85.2)	164 (64.1)	199 (77.1)	139 (53.9)
Received < 6 treatments [a]	37 (14.8)	92 (35.9)	59 (22.9)	119 (46.1)
Evaluated at Visit 9	233 (93.2)	233 (91.0)	230 (89.1)	221 (85.7)
Completed Study (Visit 10)	227 (90.8)	226 (88.3)	224 (86.8)	214 (82.9)
Did Not Complete Study	23 (9.2)	30 (11.7)	34 (13.2)	44 (17.1)
Reason fewer than maximum number of treatment sessions completed				
Insufficient SMF into which injections may safely be given	5 (2.0)	33 (12.9)	12 (4.7)	44 (17.1)
Patient satisfaction with SMF reduction	2 (0.8)	9 (3.5)	1 (0.4)	12 (4.7)
Withdrawal of consent for further treatments due to patient convenience	6 (2.4)	14 (5.5)	16 (6.2)	13 (5.0)
Withdrawal of consent for further treatments due to discomfort with procedure (Not an AE)	0	4 (1.6)	2 (0.8)	11 (4.3)
Administrative decision	4 (1.6)	5 (2.0)	3 (1.2)	9 (3.5)
Pregnancy	0	0	1 (0.4)	0
Adverse Event(s)	3 (1.2)	19 (7.4)	3 (1.2)	17 (6.6)
Lost to Follow-up	5 (2.0)	5 (2.0)	5 (1.9)	11 (4.3)
Death	0	0	0	1 (0.4)
Other [b]	12 (4.8)	3 (1.2)	16 (6.2)	1 (0.4)

	Study 22		Study 23	
	Placebo N = 250 n (%)	**ATX-101 2 mg/cm^2 N = 256 n (%)**	**Placebo N = 258 n (%)**	**ATX-101 2 mg/cm^2 N = 258 n (%)**
Patient receiving fewer than maximum number treatments due to insufficient SMF or patient satisfaction with SMF reduction				
Number of treatments received, n (%)				
5	3 (1.2)	20 (7.8)	5 (1.9)	12 (4.7)
4	1 (0.4)	10 (3.9)	3 (1.2)	25 (9.7)
3	1 (0.4)	5 (2.0)	3 (1.2)	11 (4.3)
2	1 (0.4)	6 (2.3)	2 (0.8)	5 (1.9)
1	1 (0.4)	1 (0.4)	0	3 (1.2)
Reason for Discontinuation from Study				
Administrative decision	3 (1.2)	0	0	0
Patient Noncompliance	0	1 (0.4)	1 (0.4)	1 (0.4)
Adverse Event	2 (0.8)	2 (0.8)	2 (0.8)	5 (1.9)
Lost to Follow-up	6 (2.4)	7 (2.7)	15 (5.8)	20 (7.8)
Death	0	0	1 (0.4)	1 (0.4)
Other	0	0	0	2 (0.8)
Withdrawal of consent due to patient convenience	12 (4.8)	20 (7.8)	15 (5.8)	15 (5.8)

AE = adverse event; MRI = magnetic resonance imaging; ITT = intent-to-treat; ITT-MRI = subset of ITT population who were enrolled to undergo MRI assessment; SMF = submental fat

[a] Patients who received fewer than the maximum number of treatments were encouraged to remain on study and be evaluated at 4, 12, and 24 weeks after last treatment.

[b] All but one of the "Other" category were due to dissatisfaction with treatment results.

Notes: Percentages are based on the number of ITT patients (N) in a given treatment group. Study 22 Patient 124-009 and Study 23 Patient 533-006 were randomized to placebo but received ATX-101 at Visit 4 (received placebo at all other treatment visits). For efficacy analyses, these patients are included "as randomized," per ITT, in the placebo group; for safety analyses they are included "as treated" in the ATX-101 group.

Source: Integrated Summary of Efficacy Posttext Table 3.1 in NDA 206333

4.2.5. Efficacy Results

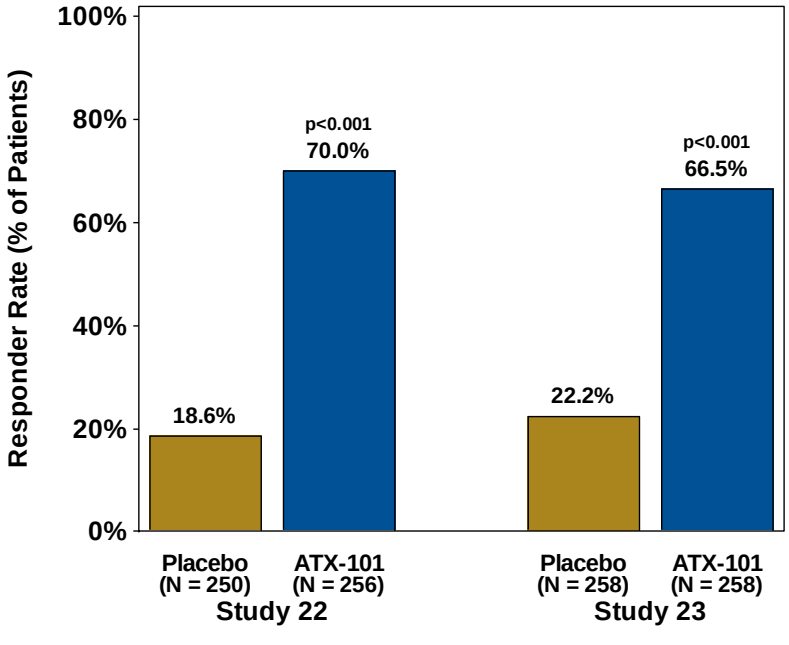
4.2.5.1. Primary Endpoints

4.2.5.1.1. Co-primary Endpoint Results

As shown in Figure 5 and Figure 6, pivotal Phase 3 Studies 22 and 23 each met their co-primary efficacy endpoints: the 1-grade composite SMFRS response rate (ie, proportion of patients with at least 1-grade simultaneous improvement in both the CR-SMFRS and the PR-SMFRS) and 2-grade composite SMFRS response rate (ie, proportion of patients with at least 2-grade simultaneous improvement in both the CR-SMFRS and the PR-SMFRS) at 12 weeks after last treatment. Specifically:

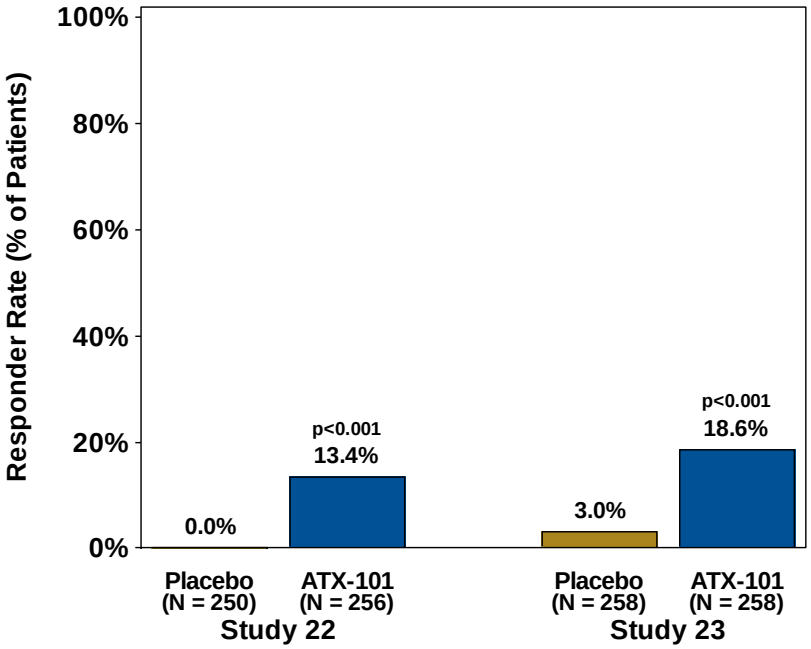
- In Study 22, a 1-grade composite SMFRS response (or greater) was obtained in 70.0% of ATX-101-treated patients compared with 18.6% of placebo-treated patients ($p < 0.001$). A 2-grade composite SMFRS response was obtained in 13.4% of ATX-101-treated patients in Study 22 compared with no placebo-treated patients ($p < 0.001$).
- In Study 23, a 1-grade composite SMFRS response was obtained in 66.5% of ATX-101-treated patients compared with 22.2% of placebo-treated patients ($p < 0.001$). A 2-grade composite SMFRS response was obtained in 18.6% of ATX-101-treated patients in Study 23 compared with 3.0% of placebo-treated patients ($p < 0.001$).

Figure 5: 1-grade Composite SMFRS Responder Rates at 12 Weeks after Last Treatment (Co-primary Endpoint) – Pivotal Studies 22 and 23



Source: Integrated Summary of Efficacy Table 3 in NDA 206333

Figure 6: 2-grade Composite SMFRS Responder Rates at 12 Weeks after Last Treatment (Co-primary Endpoint) – Pivotal Studies 22 and 23



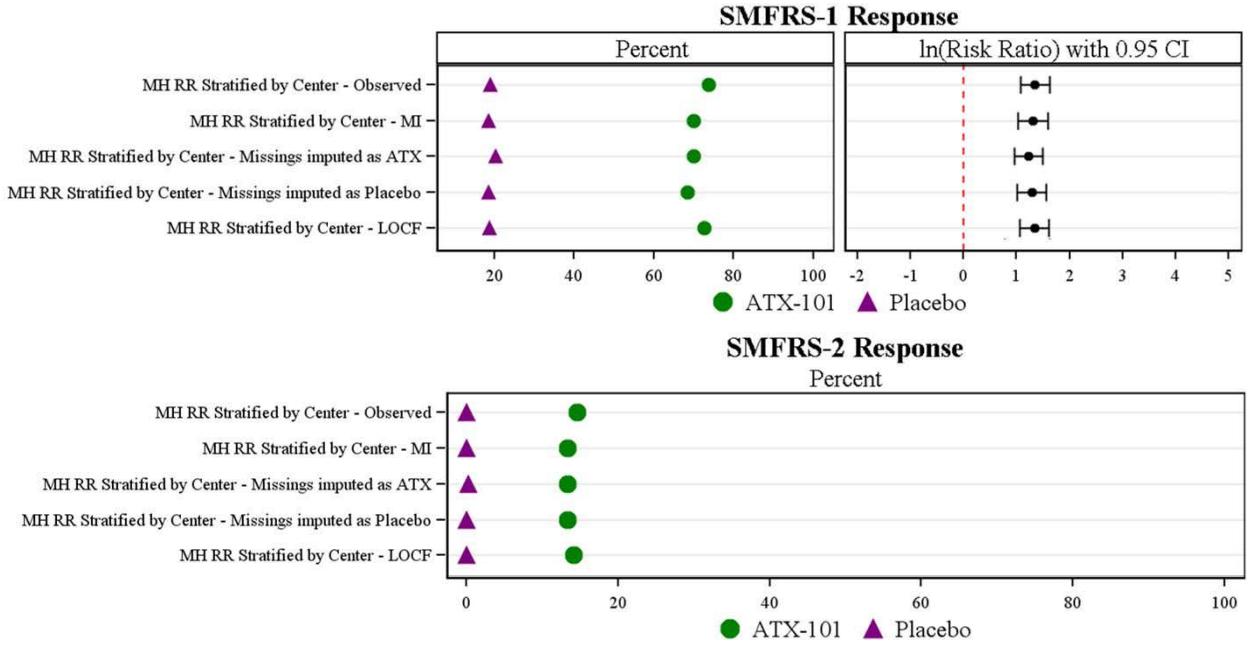
Source: Integrated Summary of Efficacy Table 3 in NDA 206333

Taken together, the results of these co-primary endpoints demonstrate a substantial treatment effect of ATX-101 in reducing the appearance of convexity or fullness associated with SMF. Representative before-and-after photographs of patients with 1-grade and 2-grade composite SMFRS responses are proved in Appendix F.

4.2.5.1.2. Co-primary Endpoint Sensitivity Analyses

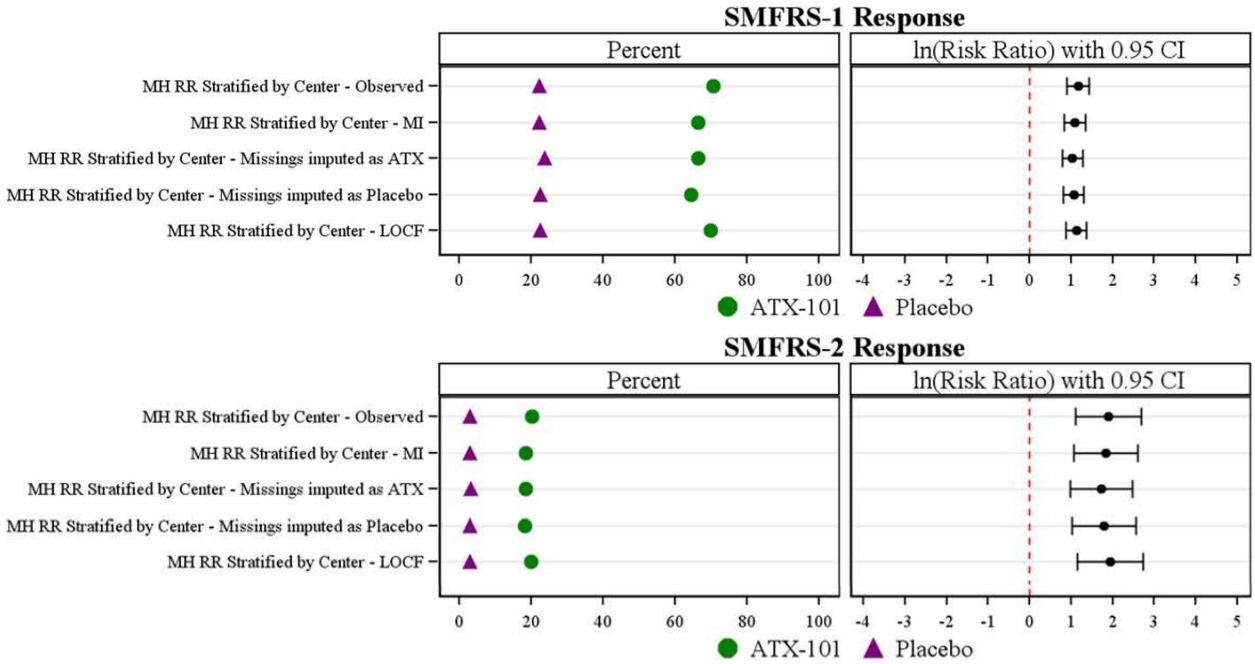
The results for the co-primary endpoints were evaluated for robustness with respect to the method of imputation of missing data and the method of analysis. Comparable and statistically significant results were observed in the prospectively defined sensitivity analyses that evaluated: 1) observed data using CMH stratified by center, 2) imputation of missing data using LOCF, 3) multiply imputing missing data with all missing patients imputed as placebo, and 4) multiply imputing missing data with all missing patients imputed as ATX-101. Results from these sensitivity analyses for Studies 22 and 23 are provided in Figure 7 and Figure 8, respectively. In addition to testing the sensitivity of the primary endpoint results to the method of imputation, secondary analyses were also performed to test the sensitivity to the method of statistical analysis. For both studies, results of observed data using logistic regression also demonstrated comparable and statistically significant results ($p < 0.001$).

Figure 7: Results of Co-primary Endpoints Sensitivity Analyses – Study 22



LOCF = last observation carry forward; MH RR = Mantel-Haenszel risk ratio; MI = multiple imputation (primary analysis) dataset; SMFRS-1 = 1-grade composite endpoint; SMFRS-2 = 2-grade composite endpoint
Note: Risk ratios not calculated for the 2-grade composite endpoint in Study 22 since there were no placebo responders.
Source: Figure 5 in Study 22 clinical study report

Figure 8: Results of Co-primary Endpoints Sensitivity Analyses – Study 23



LOCF = last observation carry forward; MH RR = Mantel-Haenszel risk ratio; MI = multiple imputation (primary analysis) dataset; SMFRS-1 = 1-grade composite endpoint; SMFRS-2 = 2-grade composite endpoint
Source: Figure 5 in Study 23 clinical study report

In order to further challenge the assertion that missing data did not meaningfully impact the statistical conclusions of the studies, post-hoc tipping point analyses were also performed. In these analyses, all combinations of missing ATX-101 and placebo patients were successively imputed as responders and non-responders, and the co-primary endpoint significance tests recalculated. The tipping-point results were consistent with the co-primary endpoint results for each study. No tipping point was observed for the 1-grade composite SMFRS response rate in either study; even in the worst-case scenario where all missing ATX-101 patients were imputed as nonresponders, and all missing placebo patients were imputed as responders, a statistically significant difference in response rate was observed ($p < 0.001$ for both studies). Similar results were obtained for the 2-grade composite response rate. In Study 22, no tipping point was observed and the worst-case scenario resulted in a statistically significant difference in response rate ($p = 0.016$). For Study 23, the majority of tipping-point scenarios yielded statistical significance; in the extreme case where all missing ATX-101 patients were imputed as nonresponders, only when 82% of the missing placebo patients were imputed as responders did results "tip" to nonsignificance ($p > 0.05$). Given the 2-grade composite placebo response rates shown above (0% to 3%), such a scenario is extremely implausible.

As noted in Section 4.2.2, patients were required to agree not to significantly change their dietary and exercise habits. Nonetheless, a small proportion of patients (< 10%) in the 2 pivotal studies lost at least 5% of their body weight during study (n = 82; 42 placebo and 40 ATX-101) and a similar number of patients (n = 86; 36 placebo and 50 ATX-101) gained at least 5% of their body weight. Therefore, a post-hoc descriptive analysis was performed using observed pooled pivotal study data to explore the impact of weight changes on the co-primary efficacy endpoints. In addition to being necessary to evaluate small subgroups, pooling of the data from these studies is considered appropriate given that the studies were conducted concurrently in the same geographic region and had identical protocols, including inclusion/exclusion criteria, treatment regimens, endpoints, and analysis methods. There was also no meaningful difference in demographics, patient disposition and results between the 2 studies. In this analysis (Table 13), comparable 1-grade and 2-grade composite SMFRS response rates were observed among patients who maintained their body weight and those who gained at least 5% body weight. As might be expected, somewhat higher response rates were observed among patients who lost at least 5% body weight. However, the numbers of these latter patients were balanced between treatment groups and, within this subgroup, an ATX-101 treatment effect remained apparent. These results indicate that patient weight loss did not substantially influence the primary efficacy conclusions of the pivotal studies.

Table 13: Primary Efficacy Results by Body Weight Change – Pooled Pivotal Studies

Co-primary Endpoints	Lost ≥ 5% Body Weight		Body Weight ± 5% of Baseline		Gained ≥ 5% Body Weight	
	Placebo N = 42	ATX-101 N = 40	Placebo N = 384	ATX-101 N = 364	Placebo N = 36	ATX-101 N = 50
Composite 1-Grade SMFRS						
Responder, n	15	33	74	259	6	36
(%)	(35.7)	(82.5)[a]	(19.3)	(71.2)[a]	(16.7)	(72.0)[a]
Composite 2-Grade SMFRS						
Responder, n	2	13	5	58	0	8
(%)	(4.8)	(32.5)[a]	(1.3)	(15.9)[a]		(16.0)[a]

[a] Fisher's exact test $p < 0.05$ versus corresponding placebo subgroup

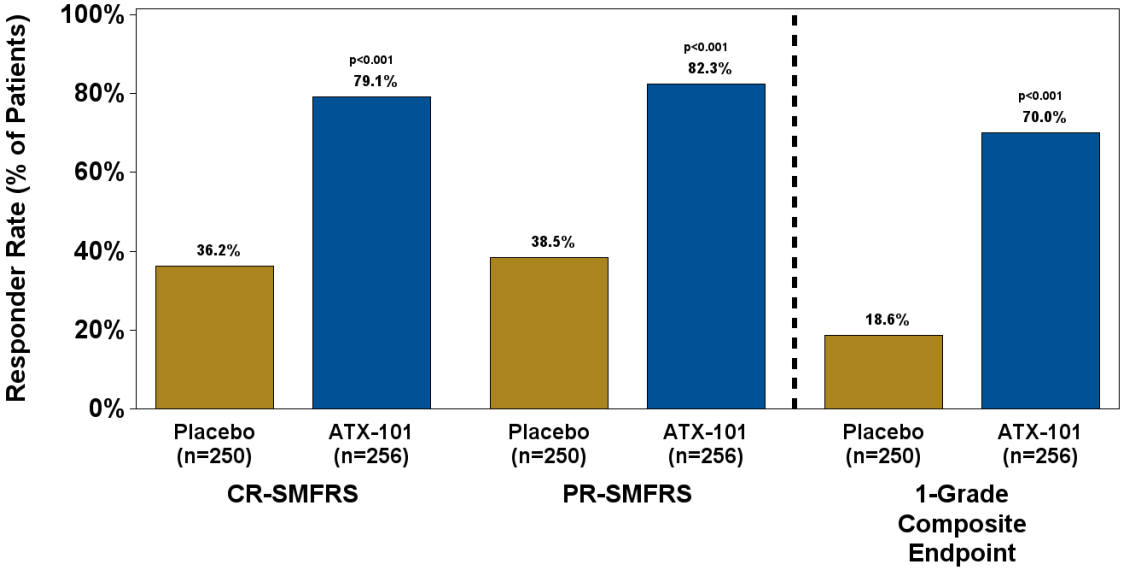
4.2.5.1.3. Components of the Composite Co-primary Endpoints

Since the co-primary endpoints are composites of the individual CR-SMFRS and PR-SMFRS responses (ie, patients must demonstrate simultaneous improvement on both the clinician rating scale and the patient rating scale to be deemed a responder), the 1-grade and 2-grade responses at 12 weeks after last treatment based on each scale individually were also summarized for each study and demonstrated statistically significant differences between ATX-101 and placebo groups ($p < 0.001$), as follows:

- 1-grade CR-SMFRS response rates were 79.1% and 77.9% for ATX-101 patients in Studies 22 and 23, respectively (compared to 36.2% and 34.5% for placebo patients)
- 1-grade PR-SMFRS response rates were 82.3% and 78.4% for ATX-101 patients in Studies 22 and 23, respectively (compared to 38.5% and 37.8% for placebo patients)
- 2-grade CR-SMFRS response rates were 38.3% and 38.7% for ATX-101 patients in Studies 22 and 23, respectively (compared to 5.0% and 9.9% for placebo patients)
- 2-grade PR-SMFRS response rates were 29.3% and 30.8% for ATX-101 patients in Studies 22 and 23, respectively (compared to 5.4% and 7.9% in placebo patients)

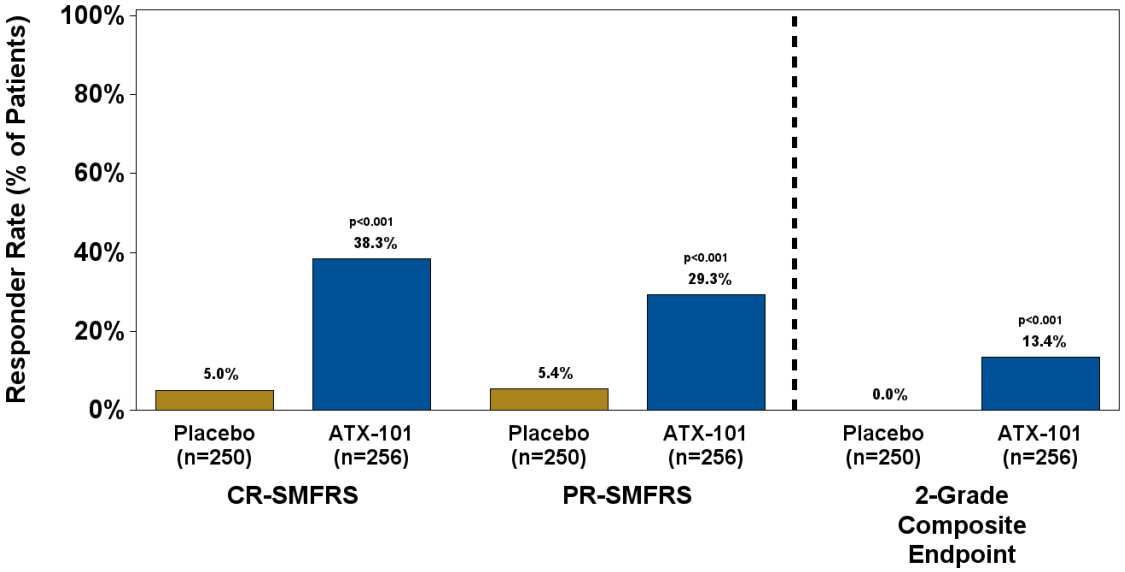
The 1-grade and 2-grade component and composite response rates are shown graphically for Study 22 in Figure 9 and Figure 10, respectively, and for Study 23 in Figure 11 and Figure 12, respectively. As noted earlier, the clinician and patient ratings of SMF reflect unique, but related, perspectives on the amount of SMF. Inspection of the figures below confirms that these 2 perspectives yield comparable results (ie, neither the patients nor the clinicians are biased toward higher response rates).

Figure 9: 1-Grade Component and Composite Responder Rates at 12 Weeks after Last Treatment (Study 22)



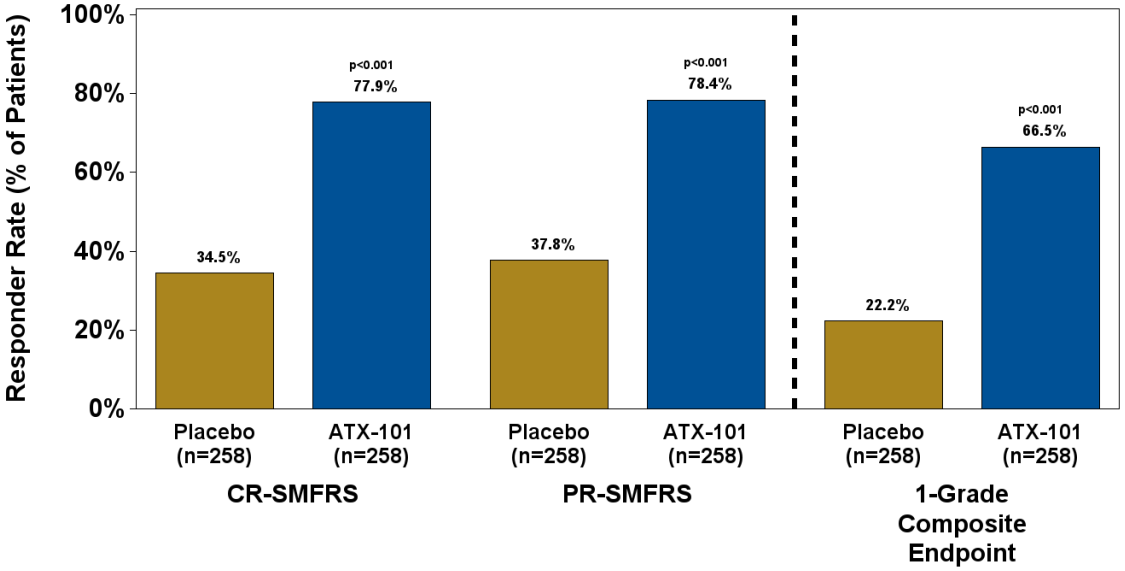
Source: Integrated Summary of Efficacy Table 3 in NDA 206333

Figure 10: 2-Grade Component and Composite Responder Rates at 12 Weeks after Last Treatment (Study 22)



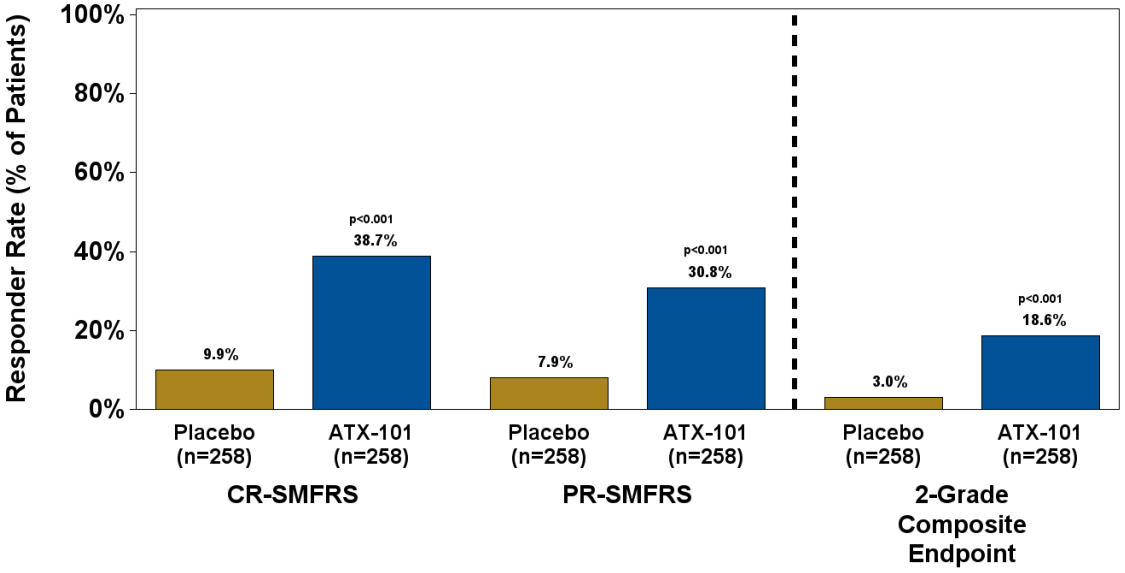
Source: Integrated Summary of Efficacy Table 3 in NDA 206333

Figure 11: 1-Grade Component and Composite Responder Rates at 12 Weeks after Last Treatment (Study 23)



Source: Integrated Summary of Efficacy Table 3 in NDA 206333

Figure 12: 2-Grade Component and Composite Responder Rates at 12 Weeks after Last Treatment (Study 23)



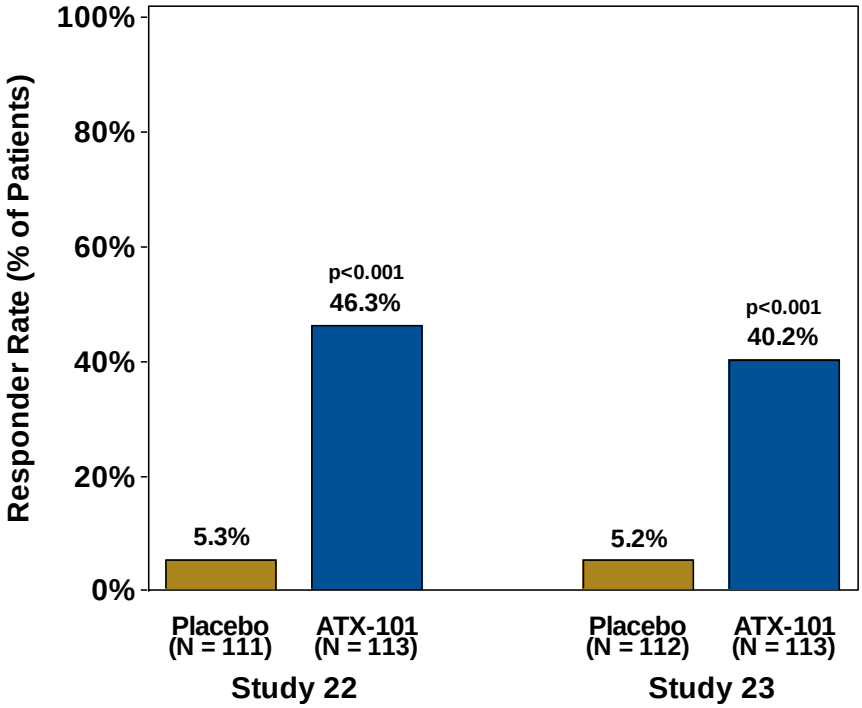
Source: Integrated Summary of Efficacy Table 3 in NDA 206333

4.2.5.2. Secondary Endpoints

4.2.5.2.1. Magnetic Resonance Imaging

As an objective measure of SMF reduction, Studies 22 and 23 included MRI assessments (as described in Section 3.3.5) in a subset of approximately 200 patients at selected sites in each study. For purposes of the secondary endpoint, an MRI responder was prospectively defined and agreed with the agency as a patient who exhibited at least a 10% reduction in volume from baseline to 12 weeks after the last treatment. Results for the MRI secondary endpoint in Studies 22 and 23 are provided in Figure 13 and show that 46.3% and 40.2% of ATX-101-treated patients were considered MRI responders in Studies 22 and 23, respectively, compared to 5.3% and 5.2% of patients treated with placebo (all $p < 0.001$).

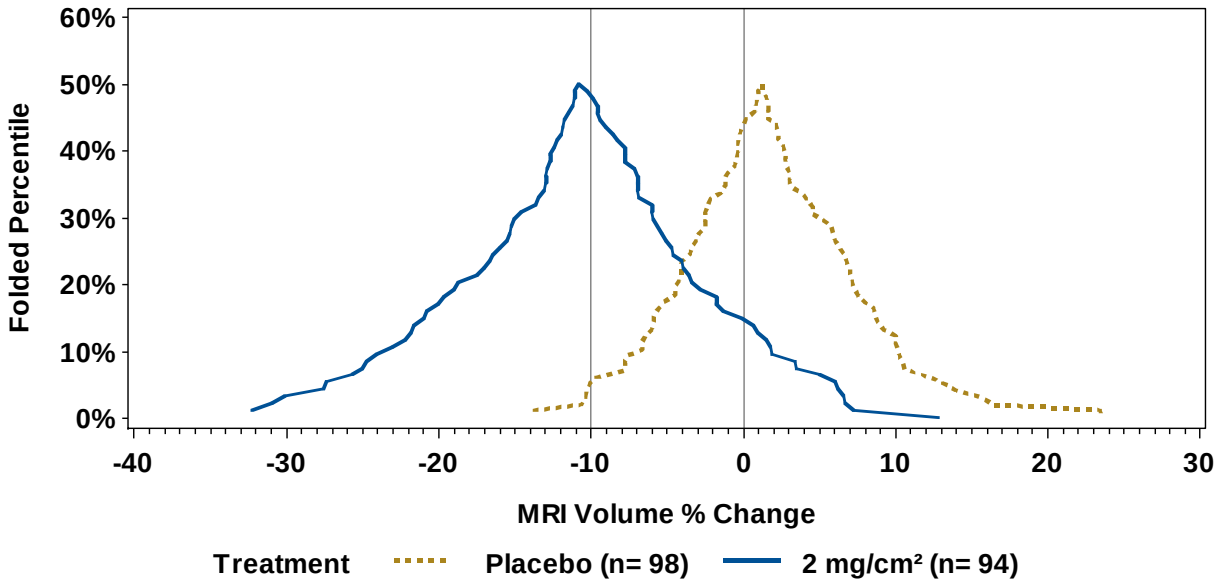
Figure 13: MRI Responder Rates at 12 Weeks after Last Treatment (Secondary Endpoint) – Pivotal Studies 22 and 23



Source: Integrated Summary of Efficacy Table 3 in NDA 206333

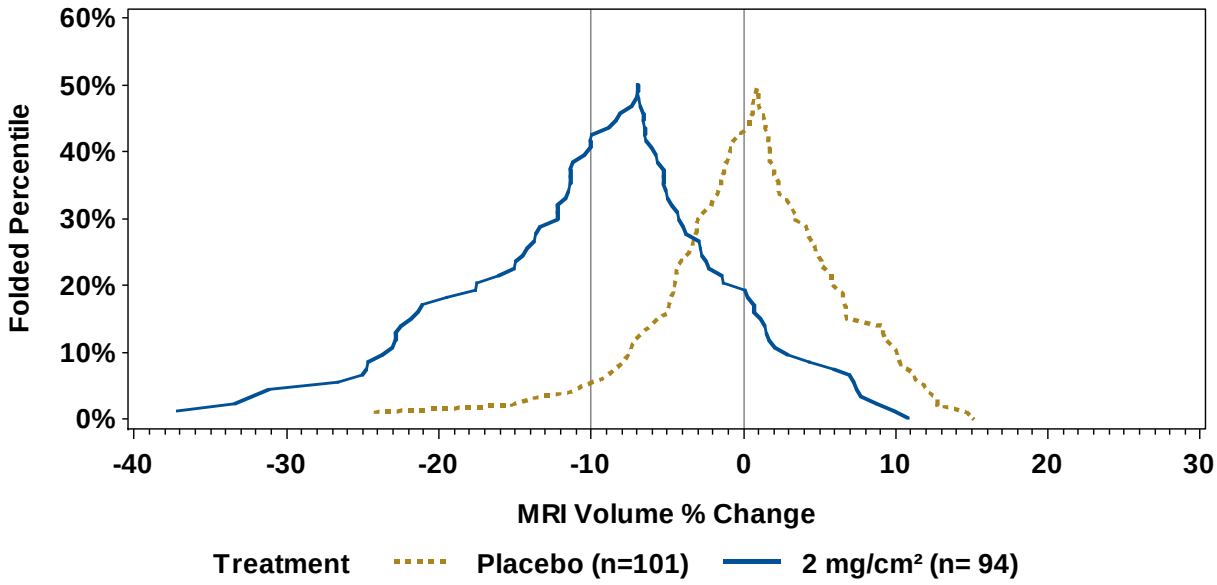
Cumulative distribution functions (folded at the 50th percentile) that display the distribution of percentage change from baseline in MRI volume by treatment group are provided for the observed data from Study 22 and Study 23 in Figure 14 and Figure 15, respectively, including reference lines for 0 (no change) and the -10% responder definition.

Figure 14: Distribution of Percentage Changes in MRI Volume (Observed Data, Study 22)



Source: Integrated Summary of Efficacy Figure 4.5.2 in NDA 206333

Figure 15: Distribution of Percentage Changes in MRI Volume (Observed Data, Study 23)



Source: Integrated Summary of Efficacy Figure 4.5.3 in NDA 206333

As was done for the co-primary endpoints, post-hoc tipping point analyses were conducted for the MRI responder data from both Studies 22 and 23. These analyses did not reveal a tipping point when missing patients were successively imputed as responders or non-responders. Even in the worst-case scenario in which all missing placebo patients were imputed as responders and

all missing ATX-101 patients were imputed as nonresponders, statistical significance in favor of ATX-101 was maintained in both studies.

4.2.5.2.2. Patient Reported SMF Impact Scale (PR-SMFIS)

The effect of treatment on patient-reported visual and emotional impact of SMF was assessed using the PR-SMFIS. The specific secondary endpoint used in the pivotal studies was the change from baseline to 12 weeks after last treatment in the PR-SMFIS total scale score (ie, an average of the 6 component items) analyzed using ANCOVA. The mean PR-SMFIS total scale scores at baseline ranged from 7.2 to 7.4 on the 0-10 scale across the treatment groups in both studies, indicating that the self-perceptions of the study populations were significantly impacted by their SMF at the start of study. In both Study 22 and Study 23, treatment with ATX-101 significantly reduced (improved) the PR-SMFIS total scale score from baseline to 12 weeks posttreatment compared to placebo. The LS mean change from baseline was -3.61 for ATX-101 vs -1.10 for placebo in Study 22 and -3.44 for ATX-101 vs -1.46 for placebo in Study 23 (all $p < 0.001$; Table 14). These changes represent approximately 47% to 50% improvement in patients treated with ATX-101, compared to approximately 15% to 20% improvement in patients treated with placebo. Additionally, the patients treated with ATX-101 had a mean change that is greater than the 3-point improvement that was established as clinically meaningful (Section 3.3.6), whereas patients treated with placebo did not.

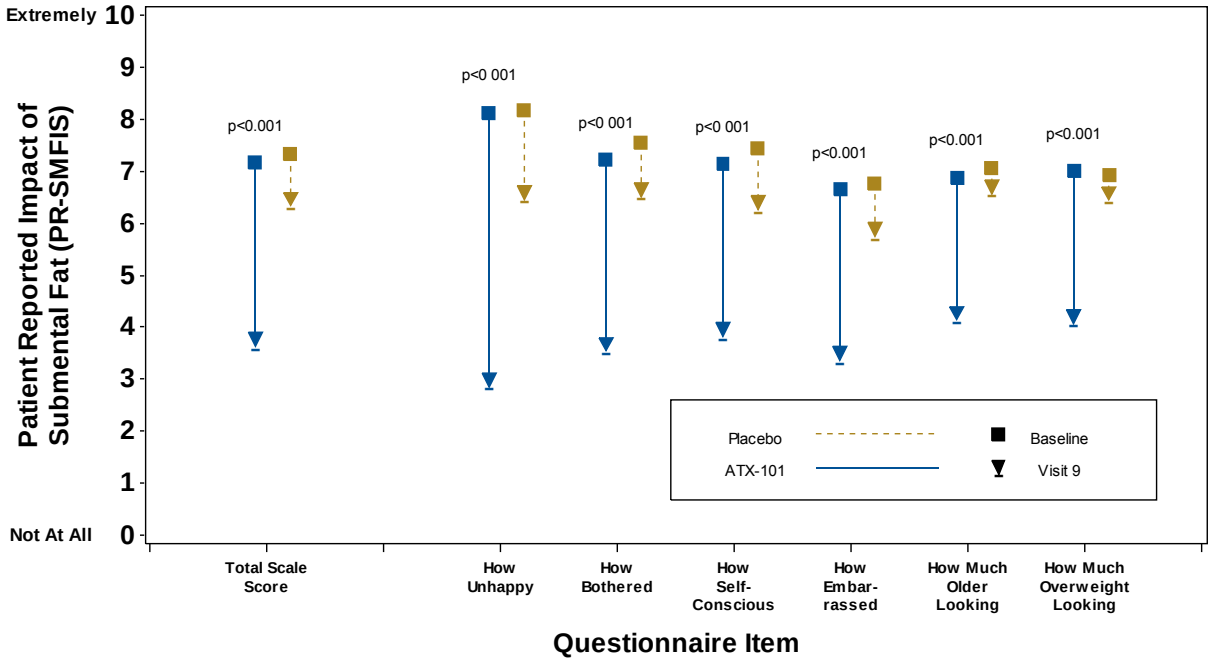
Table 14: PR-SMFIS Secondary Endpoint Results –Pivotal Studies 22 and 23

	Study 22		Study 23	
PR-SMFIS total scale score	**Placebo N = 250**	**ATX-101 N = 256**	**Placebo N = 258**	**ATX-101 N = 258**
Mean at baseline	7.33	7.17	7.24	7.37
(SD)	(1.62)	(1.69)	(1.68)	(1.72)
LS mean change from baseline	-1.10	-3.61	-1.46	-3.44
(SE)	(0.143)	(0.143)	(0.156)	(0.158)
p-value		< 0.001		< 0.001

ATX-101 = deoxycholic acid injection; LS = least squares; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; SD = standard deviation; SE = standard error
Note: Results shown are for intent-to-treat (ITT) datasets consisting of all randomized patients.
Source: Integrated Summary of Efficacy Table 12 in NDA 206333

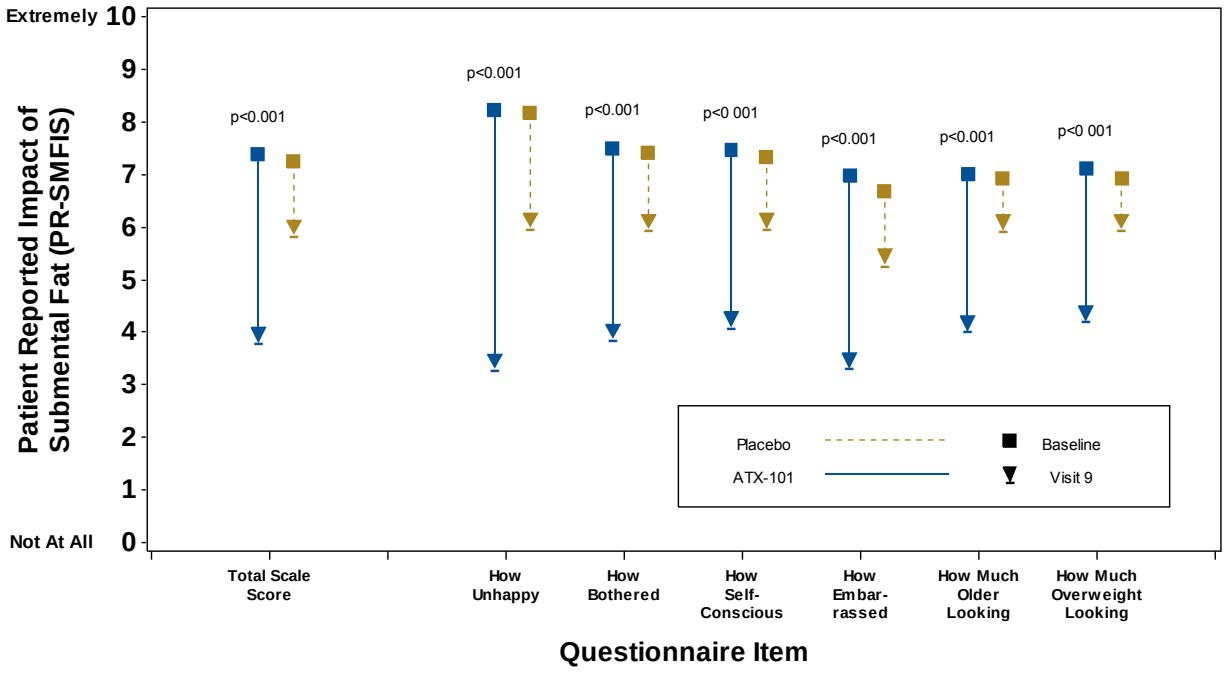
Results for the individual component items of the PR-SMFIS were evaluated using observed data and, in both Study 22 (Figure 16) and Study 23 (Figure 17), each of the 6 items demonstrated improvement in patients treated with ATX-101 compared to those treated with placebo. Patients treated with ATX-101 exhibited 42% to 67% reductions in impact ratings associated with their SMF (unhappiness, embarrassment, bother, self-consciousness, looking overweight, and looking older), compared to 8% to 28% reductions in the placebo groups (all $p < 0.001$).

Figure 16: PR-SMFIS Total Scale and Component Results (Mean) – Study 22 (Observed)



Source: Integrated Summary of Efficacy Table 12 in NDA 206333

Figure 17: PR-SMFIS Total Scale and Component Results (Mean) – Study 23 (Observed)



Source: Integrated Summary of Efficacy Table 12 in NDA 206333

Because tipping point analyses are only appropriate for responder-based analyses, they were only performed for the co-primary endpoints and the secondary MRI endpoint; no tipping-point analysis was performed for the secondary endpoint of mean change from baseline in PR-SMFIS total scale score. A post-hoc descriptive analysis of PR-SMFIS total scale score using a responder definition of 3-point improvement revealed responder rates across the pooled pivotal studies of 55.6% for ATX-101 compared to 21.2% for placebo.

4.2.5.3. Additional Endpoints

Additional prospective efficacy endpoints in pivotal Phase 3 Studies 22 and 23 included evaluations of co-primary and secondary endpoints at alternate timepoints (eg, 24 weeks after last treatment [Visit 10]) and evaluations of changes in the CR-SMFRS, PR-SMFRS and MRI (volume and thickness) as continuous measures. Other measures of efficacy were also included as prospective endpoints, including patient satisfaction with the appearance of their face/chin based on the SSRS, patient assessments of SMF based on line drawings representing each grade (ie, the PR-SMF-LD ratings), thickness of SMF measured using calipers and by MRI, and Global Questions regarding improvement in SMF, improvement in chin/neck definition, and treatment satisfaction. All of these endpoints and analyses were specified in the protocols for Studies 22 and 23 and they provide important corroborating information that supports the efficacy and benefits of ATX-101. Analyses were conducted using the ITT or ITT-MRI data for endpoints that had multiply imputed data available (ie, the CR-SMFRS, PR-SMFRS, PR-SMFIS and MRI); however, since no adjustments are made for multiplicity the resulting p-values should be considered descriptive in nature.

Results for the additional efficacy endpoints are summarized in Table 15 and demonstrate significant improvements associated with treatment with ATX-101 for the following:

1. Composite and component 1-grade and 2-grade CR-SMFRS and PR-SMFRS responses at 24 weeks after last treatment session. The proportions of patients in each treatment group who had 1-grade and 2-grade responses at the end-of-study timepoint (Visit 10) were also similar to those observed at the co-primary endpoints at 12 weeks after the last treatment (Visit 9).
2. Mean change from baseline in both the CR-SMFRS score and the PR-SMFRS score at 12 weeks after last treatment (Visit 9). The mean changes from baseline were -1.3 (CR-SMFRS) and -1.1 to -1.2 (PR-SMFRS) in the ATX-101 group compared with -0.3 to -0.4 for these measures in the placebo groups (all $p < 0.001$). These data suggest that, as a group, patients who received ATX-101 had a clinically meaningful (≥ 1 grade) reduction in SMF, whereas patients who received placebo did not.
3. Mean change from baseline (percentage change) in MRI assessments of SMF volume and thickness. In the pivotal studies, SMF volume was reduced by an LS mean of 6.7% to 9.1% in ATX-101-treated patients compared to a 1.1% to 1.9% increase in placebo-treated patients. Similar changes (-8.5% to -18.4% for ATX-101 versus +0.9% to +1.3% for placebo) were observed for SMF thickness as assessed by MRI.
4. Impacts of SMF as assessed by PR-SMFIS total scale score at 24 weeks after last treatment (Visit 10). The LS mean changes from baseline to 24 weeks after the last treatment were -3.57 to -3.68 for the ATX-101 groups and -0.91 to -1.50 for the placebo

groups (all $p < 0.001$). These results were comparable to those observed at the primary evaluation at 12 weeks after last treatment (Visit 9).

5. Patient satisfaction with appearance of their face and chin, as assessed by SSRS response at 12 and 24 weeks after last treatment. An enrollment criterion in pivotal Studies 22 and 23 required that patients be at least slightly dissatisfied with the appearance of their face/chin (SSRS rating ≤ 2) and a responder was defined as being at least slightly satisfied at Visit 9 (SSRS rating ≥ 4). Results demonstrated that a high proportion of patients were satisfied with the appearance of their face/chin following treatment with ATX-101. At the end of study (Visit 10), 77.1% to 81.1% of patients in the ATX-101 groups were SSRS responders, compared to 27.3% to 38.4% of patients in the placebo groups (all $p < 0.001$).
6. Changes in caliper measurements of SMF thickness at 12 and 24 weeks after last treatment. Unlike MRIs, which were conducted in a subset of about 200 patients at selected centers in each pivotal study, all patients at all centers in Studies 22 and 23 had the thickness of their SMF measured at baseline and posttreatment using calipers. The LS mean percent changes from baseline in thickness of SMF assessed using calipers at 12 and 24 weeks after the last treatment session in the ATX-101 groups were -17.8% to -21.9% and -22.5% to -24.9%, respectively. At these same respective time points, the LS mean percent changes from baseline in thickness of SMF in the placebo group were -6.2% to -8.4% and -7.7% to -8.4% ($p < 0.001$ for all comparisons).
7. Mean change from baseline in patient assessments of SMF based on line drawings of each rating (ie, PR-SMF-LD ratings). The mean changes from baseline to 12 weeks after last treatment in PR-SMF-LD ratings were -1.2 to -1.4 in the ATX-101 groups and -0.3 to -0.4 in the placebo groups (all $p < 0.001$), very comparable to the mean CR-SMFRS and PR-SMFRS changes shown in #2 above.
8. Responses to Global Questions related to improvement in SMF, improvement in definition between the chin and neck, and satisfaction with treatment. For these questions (Appendix E), patients were considered responders if they reported that their SMF or chin/neck definition was at least "moderately better," or if they responded that they were at least "moderately satisfied" with treatment. For all 3 questions, a high proportion of ATX-101 patients reported at least moderate improvement/satisfaction (67.4% to 77.8%), compared to placebo patients (16.2% to 33.9%), all $p < 0.001$.

In every analysis, the results of the additional endpoints supported the conclusions drawn from the co-primary and secondary endpoint analyses, and further confirmed the superiority and benefits of ATX-101 relative to placebo in reducing SMF.

Table 15: Additional Efficacy Endpoint Results – Pivotal Studies 22 and 23

Endpoint[a]	Study 22		Study 23	
	Placebo	ATX-101[b]	Placebo	ATX-101[b]
Composite 1-grade SMFRS response (Visit 10)	16.8%	69.3%	22.4%	68.4%
1-grade CR-SMFRS response (Visit 10)	33.7%	78.5%	34.7%	78.3%
1-grade PR-SMFRS response (Visit 10)	36.1%	82.1%	42.3%	79.4%
Composite 2-grade SMFRS response (Visit 10)	0	17.4%	2.1%	19.5%
2-grade CR-SMFRS response (Visit 10)	3.8%	40.4%	10.3%	41.3%
2-grade PR-SMFRS response (Visit 10)	3.1%	30.7%	7.5%	29.7%
CR-SMFRS mean change (Visit 9)	-0.4	-1.3	-0.4	-1.3
PR-SMFRS mean change (Visit 9)	-0.3	-1.2	-0.4	-1.1
MRI volume mean % change (Visit 9)	+1.9%	-9.1%	+1.1%	-6.7%
MRI thickness mean % change (Visit 9)	+0.9%	-18.4%	+1.3%	-8.5%
PR-SMFIS total scale score mean change (Visit 10)	-0.91	-3.68	-1.50	-3.57
SSRS response (≥ 4 at Visit 9/Visit 10)	31.0%/27.3%	82.8%/81.1%	36.2%/38.4%	75.1%/77.1%
Caliper thickness mean % change (Visit 9/Visit 10)	-6.2%/-7.7%	-21.9%/-24.9%	-8.4%/-8.4%	-17.8%/-22.5%
PR-SMF-LD mean change (Visit 9)	-0.3	-1.4	-0.4	-1.2
Global Questions:				
#1. Impression of change response (≥ "moderately better")	16.6%	74.7%	24.7%	70.7%
#2. Chin/neck definition response (≥ "moderately better")	16.2%	68.9%	21.6%	67.4%
#3. Treatment satisfaction response (≥ "moderately satisfied")	30.3%	77.8%	33.9%	75.3%

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; MRI = magnetic resonance imaging; PR-SMFIS = Patient-Reported Submental Fat Impact Scale; PR-SMF-LD = Patient-Reported Submental Fat Line Drawing assessment; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; SMFRS = Submental Fat Rating Scale (composite of CR-SMFRS and PR-SMFRS); SSRS = Subject Self-Rating Scale

Notes: Visit 9 is the primary endpoint evaluation at 12 weeks after last treatment; Visit 10 is final study visit at 24 weeks after last treatment

[a] All "mean" values are analysis of covariance least squares means.

[b] All results $p < 0.001$ compared to corresponding placebo.

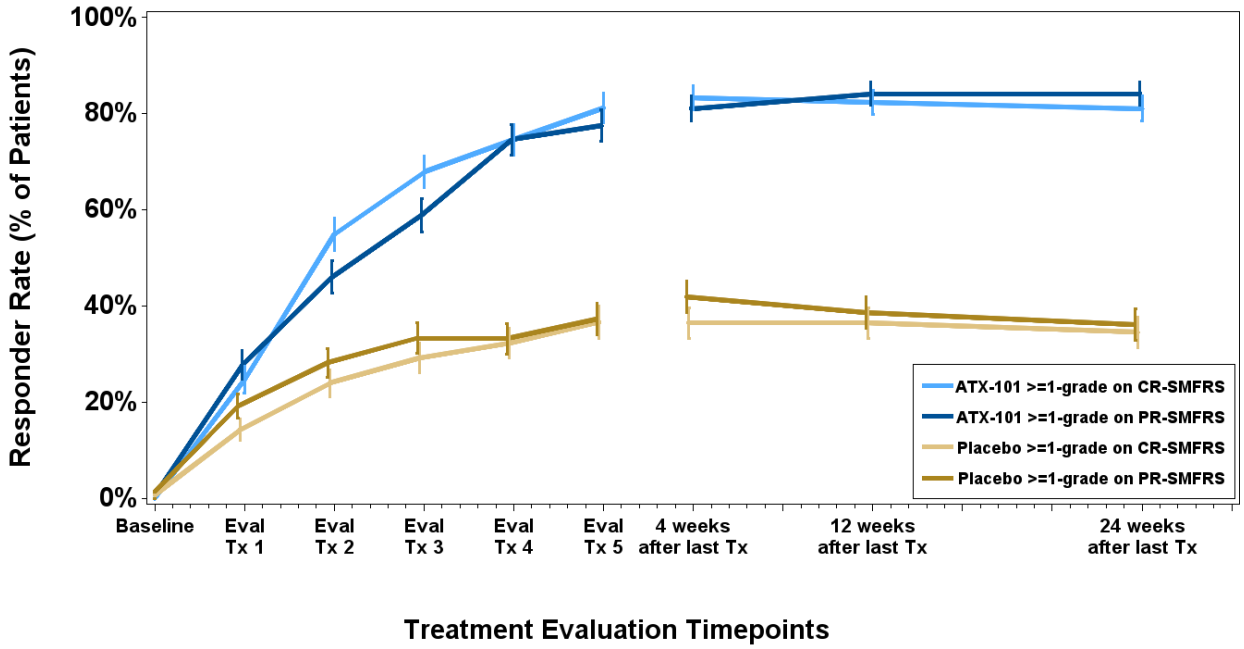
Source: Integrated Summary of Efficacy Posttext Tables 4.1.1.2, 4.2.1.1, 4.2.1.2, 4.3.1.1, 4.3.1.2, 4.4.1.1, 4.5.1.2, 4.6.1, 4.7.1, 4.8.1.1, 4.9.1 in NDA 206333; Table 21 in clinical study reports for Studies 22 and 23

4.2.5.4. Additional Analyses

4.2.5.4.1. Number of Treatments to Achieve Response

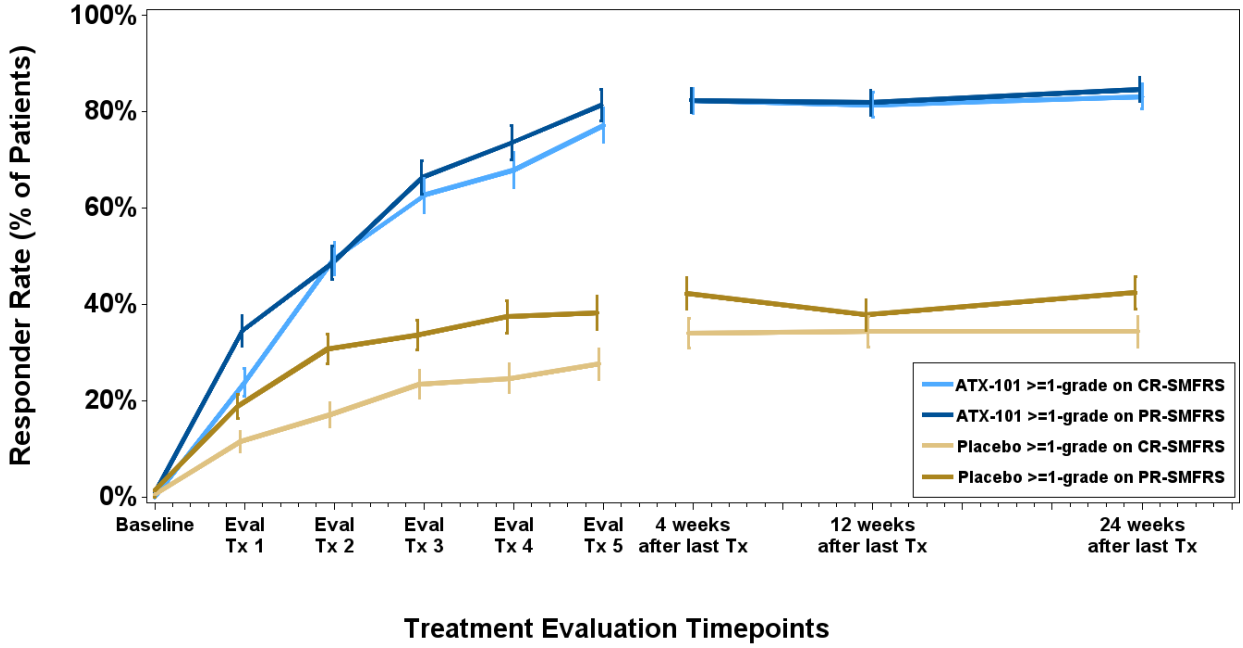
The response rate following each treatment was also described using the pivotal study data in order to identify the number of treatments needed to achieve observable responses (ie, 1-grade CR-SMFRS and 1-grade PR-SMFRS). For the purpose of this analysis, a patient was deemed a responder following a given treatment only if they went on to also be a responder at 12 weeks after last treatment (ie, the primary endpoint assessment timepoint). Observed response rates over the course of treatment for Study 22 (Figure 18) and Study 23 (Figure 19) suggest that similar numbers of treatments (median of 2 to 3) are required to achieve responses that are observable by the clinician (1-grade CR-SMFRS) or the patient (1-grade PR-SMFRS). To provide further elucidation, censored time-to-event (survival) analyses were also conducted to estimate the number of treatments to achieve first response. Based on these survival analyses, the median numbers of treatments to achieve a 1-grade CR-SMFRS response in the ATX-101 group in pivotal Studies 22 and 23 were 2 and 3, respectively. Similarly, the number of treatments to achieve a 1-grade PR-SMFRS response was 3 for ATX-101-treated patients in each study.

Figure 18: 1-Grade CR-SMFRS and PR-SMFRS Response by Treatment – Study 22 Observed Data (ITT Analysis Set)



ATX-101 = deoxycholic acid injection; CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; Eval = evaluation at 4 weeks after the indicated treatment; ITT = intent-to-treat; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; Tx = treatment.
Note: Error bars indicate standard errors; $p < 0.001$ for ATX-101 vs placebo at all timepoints.
Source: Integrated Summary of Efficacy Posttext Tables 4.2.1.2 and 4.3.1.2 of NDA 206333

Figure 19: 1-Grade CR-SMFRS and PR-SMFRS Response by Treatment – Study 23 Observed Data (ITT Analysis Set)



ATX-101 = deoxycholic acid injection; CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; Eval = evaluation at 4 weeks after the indicated treatment; ITT = intent-to-treat; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; Tx = treatment
Note: Error bars indicate standard errors; $p < 0.001$ for ATX-101 vs placebo at all timepoints.
Source: Integrated Summary of Efficacy Posttext Tables 4.2.1.2 and 4.3.1.2 of NDA 206333

Together, these results indicate that improvements in SMF were typically visible to the clinician (1-grade CR-SMFRS) and/or the patient (1-grade PR-SMFRS) after a median of 2 to 3 treatment sessions. As previously noted, such 1-grade improvements are associated with at least moderate global improvement and a high level of patient satisfaction.

4.2.5.4.2. Comparison of Efficacy Results in Subpopulations

The co-primary efficacy endpoint results for pivotal Phase 3 Studies 22 and 23 (ie, the 1-grade and 2-grade composite SMFRS responder analyses at 12 weeks after the last treatment session) were evaluated in within subgroups based on age, sex, race, ethnicity, baseline SMF ratings, baseline BMI, and baseline SMSLG. Subgroup results for pooled data across the pivotal studies are presented in Table 16. As with the weight-change analysis discussed earlier, pooling was utilized in order to evaluate potentially small subgroups and is considered appropriate given that the 2 studies were conducted concurrently in the same geographic region, used identical protocols, and demonstrated no meaningful differences in demographics, patient disposition and results. The results of the subgroup analyses consistently favored ATX-101 relative to placebo regardless of demographics or other baseline characteristics. A notable exception was for the 2-grade composite endpoint in nonwhites; however, the low response rate for this endpoint in general and the relatively small number of patients in the subgroup make interpretation difficult. When considering the 1-grade composite endpoint, nonwhite patients treated with ATX-101 demonstrated a significantly higher response rate (62.5%) compared to their counterparts treated with placebo (26.9%).

Table 16: Comparison of Efficacy Results by Subgroup - Studies 22 and 23 (Pooled)

Demographic/ Baseline Subgroup	1-grade Composite SMFRS Response		2-grade Composite SMFRS Response	
	Placebo	ATX-101	Placebo	ATX-101
Age < 50	45/227 (19.8%)	147/205 (71.7%)[a]	6/227 (2.6%)	33/205 (16.1%)[a]
Age ≥ 50	50/236 (21.2%)	181/249 (72.7%)[a]	1/236 (0.4%)	46/249 (18.5%)[a]
Female	89/393 (22.6%)	281/381 (73.8%)[a]	7/393 (1.8%)	72/381 (18.9%)[a]
Male	6/70 (8.6%)	47/73 (64.4%)[a]	0/70	7/73 (9.6%)[a]
Race = White	81/411 (19.7%)	288/390 (73.8%)[a]	5/411 (1.2%)	77/390 (19.7%)[a]
Race = Nonwhite	14/52 (26.9%)	40/64 (62.5%)[a]	2/52 (3.8%)	2/64 (3.1%)
Non-Hispanic	81/412 (19.7%)	288/394 (73.1%)[a]	5/412 (1.2%)	66/394 (16.8%)[a]
Hispanic/Latino	14/51 (27.5%)	40/60 (66.7%)[a]	2/51 (3.9%)	13/60 (21.7%)[a]
CR-SMFRS = 2	48/241 (19.9%)	159/225 (70.7%)[a]	1/241 (0.4%)	31/225 (13.8%)[a]
CR-SMFRS = 3	47/222 (21.2%)	169/229 (73.8%)[a]	6/222 (2.7%)	48/229 (21.0%)[a]
PR-SMFRS = 2	56/288 (19.4%)	200/288 (69.4%)[a]	0/288	27/288 (9.4%)[a]
PR-SMFRS = 3[b]	39/175 (22.3%)	128/166 (77.1%)[a]	7/175 (4.0%)	52/166 (31.3%)[a]
BMI ≤ 30 kg/m^2	58/279 (20.8%)	205/272 (75.4%)[a]	3/279 (1.1%)	55/272 (20.2%)[a]
BMI > 30 kg/m^2	37/184 (20.1%)	123/182 (67.6%)[a]	4/184 (2.2%)	24/182 (13.2%)[a]
Laxity ≤ Mild	73/383 (19.1%)	269/376 (71.5%)[a]	6/383 (1.6%)	65/376 (17.3%)[a]
Laxity ≥ Moderate	22/80 (27.5%)	59/78 (75.6%)[a]	1/80 (1.3%)	14/78 (17.9%)[a]

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale
[a] CMH $p < 0.05$ versus corresponding placebo subgroup
[b] Includes 1 placebo patient in Study 22 with a baseline PR-SMFRS rating of 4.
Source: Integrated Summary of Efficacy Posttext Tables 4.10.1.1 to 4.10.1.8 in NDA 206333

4.3. Supportive European Phase 3 Studies

Supportive Studies 16 and 17 were Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in which at least 360 patients in each study were planned to be randomized in a 1:1:1 ratio to receive up to 4 treatments with 1 mg/cm^2 ATX-101 (5 mg/mL), 2 mg/cm^2 ATX-101 (10 mg/mL), or placebo to evaluate the efficacy of each dose of ATX-101 in reducing SMF. Both of these studies were conducted in the EU and were initiated prior to completion of Phase 2 Study 15, hence, the inclusion of 2 doses of ATX-101. Patients who successfully completed screening and baseline evaluations received up to 10 mL of study drug per treatment session, administered in 0.2-mL injections spaced on a 1-cm grid, depending upon the size and configuration of the SMF. Treatment was given at 28-day (± 5 days) intervals.

The primary efficacy objective in both studies was to evaluate the effects of 1 and 2 mg/cm^2 ATX-101 SC injections in the submental area, relative to placebo, for the reduction of SMF and for patient satisfaction. The clinician rating scale (CR-SMFRS) was used to evaluate the reduction of SC fat in the submental area (improved convexity/fullness), and the SSRS was used to evaluate patient satisfaction with appearance in association with their face and chin.

Specifically, the co-primary efficacy endpoints in these studies were the percentage of patients with at least a 1-grade improvement from baseline to 12 weeks after the last treatment in the CR-SMFRS, and the percentage of patients with a SSRS rating of 4 or higher (at least slightly satisfied) 12 weeks after the last treatment. The secondary efficacy endpoints included the percentages of patients with at least 2-grade improvements from baseline in the CR-SMFRS, changes from baseline in assessments of caliper measurements of the submental area, and patient-reported outcomes using the patient rating scale (PR-SMFRS), the impact scale (PR-SMFIS), and other patient-reported assessments.

Each of these 2 supportive Phase 3 studies met their primary endpoints, showed statistically significant improvements in secondary endpoints, and demonstrated that both doses of ATX-101 were superior to placebo in the reduction of SMF, as measured by the clinician (CR-SMFRS), the patient (SSRS, PR-SMFRS, PR-SMFIS, etc.), and objective measures (calipers). Higher response rates were observed with the higher dose (ie, 2 mg/cm^2). A summary of the efficacy results is presented in Table 17.

Table 17: Prespecified Efficacy Results for Supportive EU Phase 3 Studies 16 and 17

	Endpoints	ATX-101-10-16 N = 363 randomized	ATX-101-10-17 N = 360 randomized
Primary Efficacy Endpoints	*1-grade CR-SMFRS responder at 12 weeks after the last treatment*:	Placebo = 23.0% ATX-101 (1 mg/cm^2) = 59.2% ATX-101 (2 mg/cm^2) = 65.3% (All p < 0.001)	Placebo = 34.5% ATX-101 (1 mg/cm^2) = 58.3% ATX-101 (2 mg/cm^2) = 62.3% (p < 0.001)
	SSRS responder at 12 weeks after the last treatment:	Placebo = 28.7% ATX-101 (1 mg/cm^2) = 53.3% ATX-101 (2 mg/cm^2) = 66.1% (All p < 0.001)	Placebo = 29.3% ATX-101 (1 mg/cm^2) = 68.3% ATX-101 (2 mg/cm^2) = 64.8% (p < 0.001)
Key Secondary Efficacy Endpoints	*2-grade CR-SMFRS responder at 12 weeks after the last treatment:*	Placebo = 1.6% ATX-101 (1 mg/cm^2) = 9.2% (p = 0.009) ATX-101 (2 mg/cm^2) = 17.4% (p < 0.001)	Placebo = 0.9% ATX-101 (1 mg/cm^2) = 9.2% (p = 0.005) ATX-101 (2 mg/cm^2) = 9.0% (p = 0.004)
	1-grade PR-SMFRS responder at 12 weeks after the last treatment:	Placebo = 32.3% ATX-101 (1 mg/cm^2) = 69.7% ATX-101 (2 mg/cm^2) = 76.0% (All p < 0.001)	Placebo = 39.5% ATX-101 (1 mg/cm^2) = 60.5% ATX-101 (2 mg/cm^2) = 61.2% (All p < 0.001)
	PR-SMFIS total scale scores at 12 weeks after the last treatment:	LSM, placebo = -0.9 ATX-101 (1 mg/cm^2) = -2.3 ATX-101 (2 mg/cm^2) = -3.1 (All p < 0.001)	LSM, placebo = -1.3 ATX-101 (1 mg/cm^2) = -2.7 ATX-101 (2 mg/cm^2) = -2.7 (All p < 0.001)
	Change from baseline in thickness of SMF by caliper measurement at 12 weeks after the last treatment:[a]	Mean (mm), placebo = -1.6 ATX-101 (1 mg/cm^2) = -3.6 ATX-101 (2 mg/cm^2) = -3.9 (All p < 0.001)	Mean (mm), placebo = -2.5 ATX-101 (1 mg/cm^2) = -3.4 ATX-101 (2 mg/cm^2) = -3.6 (All p < 0.001)

CR-SMFRS = Clinician-reported Submental Fat Rating Scale; LSM = least squares mean; PR-SMFIS = Patient-reported Submental Fat Impact Scale; PR-SMFRS = Patient-reported Submental Fat Rating Scale; SSRS = Subject Self Rating Scale

[a] Studies specified caliper changes in mm. Percentage changes from baseline for placebo groups ranged from -7.1% to -13.8% and for ATX-101 groups ranged from -19.0% to -21.3%

Source: Integrated Summary of Efficacy Table 4 of NDA 206333

The primary and secondary endpoints used in pivotal Phase 3 Studies 22 and 23 were also applied to the data from the supportive EU Phase 3 studies. Pooled results shown in Table 18 indicate that 49.0% of 2 mg/cm^2 ATX-101-treated patients and 41.3% of 1 mg/cm^2 ATX-101-treated patients had at least a 1-grade composite SMFRS response compared with 15.5% of placebo-treated patients ($p < 0.001$ for both doses). The higher dose of ATX-101 (2 mg/cm^2) also resulted in statistically significant 2-grade composite SMFRS responses compared to placebo (7.5% versus 0.4%, $p < 0.001$); however, the 1 mg/cm^2 dose did not (1.7% versus 0.4%, $p = 0.203$). Both doses of ATX-101 resulted in improvements in the impacts of SMF as assessed by the PR-SMFIS total scale score. The somewhat lower response rates and mean PR-SMFIS changes observed in these EU studies compared with the pivotal studies are consistent with fewer treatments with ATX-101 (maximum of 4 versus a maximum of 6 in the pivotal studies).

Table 18: Exploratory Pivotal Endpoint Results - Supportive Studies 16/17 (Pooled)

	Endpoint	Placebo N = 238	ATX-101 1 mg/cm^2 N = 240	ATX-101 2 mg/cm^2 N = 243
Co-primary	1-Grade Composite SMFRS, N	233	235	241
	Responder, n	36	97	118
	(%)	(15.5)	(41.3)	(49.0)
	p-value		< 0.001	< 0.001
	2-Grade Composite SMFRS, N	233	235	241
	Responder, n	1	4	18
	(%)	(0.4)	(1.7)	(7.5)
	p-value		0.203	< 0.001
Secondary	MRI Volume (≥ 10% reduction)	NA	NA	NA
	PR-SMFIS total scale score, N	213	217	217
	LS mean change from baseline	-1.1	-2.5	-2.9
	(SE)	(0.14)	(0.14)	(0.14)
	p-value		< 0.001	< 0.001

Notes: Composite SMFRS responder results are based on ITT datasets with imputation of missing values using last observation carried forward (LOCF), analyzed by Cochran-Mantel-Haenszel (CMH) test stratified by center. PR-SMFIS (analyzed using ANCOVA) are based on observed data.
Source: Integrated Summary of Efficacy Tables 14 and 15 in NDA 206333

4.4. Long-term Follow-up Studies

The mechanism of action of ATX-101 described in Section 2.2 (ie, adipocytolysis - the permanent destruction of fat cells), suggests that its effects will be long-lasting and that retreatment of SMF is likely to be unnecessary. This conclusion is further supported by the persistence of efficacy (ie, maintenance of response) observed in LTFU of patients treated with ATX-101 in clinical studies. In addition to the 24-week posttreatment data from pivotal Studies 22 and 23 (Section 4.2.5.3), such LTFU efficacy results are available from the following clinical studies:

- Completed Study 26, an open-label treatment and LTFU study which included 12 months of follow-up after last treatment for all patients.

- Three additional LTFU studies that enrolled and followed patients who had completed treatment with ATX-101 or placebo in an earlier Phase 2 or 3 Study:
  - Ongoing Study 12, a nontreatment study collecting LTFU data for up to 5 years after the last treatment in patients who were treated in a previous Kythera-sponsored Phase 2 SMF study (Studies 03, 07, and 15). Each of these predecessor studies was blinded and placebo-controlled; investigators and patients were not informed of their prior treatment group assignment.
  - Completed Study 1403740, a nontreatment study that collected LTFU data for up to 2 years after the last visit in a prospective subset of approximately 200 patients from selected sites in supportive EU Phase 3 Studies 16 and 17. As with Study 12, investigators and patients remained blinded to prior treatment group assignment during the follow-up period.
  - Ongoing Study 35, a nontreatment study collecting LTFU data for up to 3 years after the last treatment in a subset of patients who participated in the pivotal Phase 3 Studies 22 and 23. Data were not yet available from this study at the time of ATX-101 NDA submission; therefore, no data are provided herein.

Persistence of efficacy was primarily analyzed based on proportion of responders at 12 weeks after last treatment (eg, in the predecessor study for patients in Study 12 and Study 1403740) who were still responders at the LTFU timepoint being examined. For this purpose, responders were considered based on 1-grade improvements in the CR-SMFRS, PR-SMFRS and the Composite SMFRS. Note that early Studies 03 and 07 did not include the PR-SMFRS, so PR-SMFRS and composite SMFRS results for Study 12 are derived solely from patients treated in later Phase 2 Study 15. It should also be noted that the analyses in the 3 studies differed in that the denominators in Study 26, which included both treatment and LTFU, were based on the numbers of responding patients in the study (regardless of whether they attended the assessment visit), while the denominators in Studies 12 and 1403740 were based on the numbers of responding patients who attended the assessment visit, since not all patients in the predecessor studies consented to enrollment in Studies 12 and 1403740 and not all patients attended (or would have been eligible to attend) every visit.

Nonetheless, the results from the 3 studies were comparable and showed a high persistence of efficacy over time, as evidenced by the data in Table 19. For example, at the 1-year timepoint common to all studies, maintenance of response (based on the 1-grade CR-SMFRS response) in ATX-101 treated patients was 90.4% in Study 26, 93.9% in Study 12, and 85.0% and 87.0% for the 1 mg/cm^2 and 2 mg/cm^2 ATX-101 dose groups, respectively, in Study 1403740. Results at the 2-year follow-up in Studies 12 and 1403740 were also consistent for patients treated with ATX-101, demonstrating maintenance of 1-grade CR-SMFRS responses in 87.0% to 91.7% of patients. At the longest follow-up timepoint with available data (ongoing Study 12), 4 years after treatment in the early Phase 2 studies, 1-grade CR-SMFRS responses were observed to have been maintained in 29 of the 33 responders (87.9%) who attended the 4-year visit. Similar results were observed for maintenance of 1-grade PR-SMFRS and 1-grade composite responses through 2 years; data were unavailable for these endpoints at 3 and 4 years (Table 19).

Overall, based on the mechanism of action of ATX-101, the results of LTFU in Studies 26, 12, and 1403470, as well as analyses conducted 24 weeks after the last treatment session in the

pivotal Phase 3 studies, it can be concluded that reductions in SMF following treatment with ATX-101 are sustained, and have been observed to be maintained for as long as 4 years.

Table 19: Maintenance of Response Results from LTFU Studies

Time-point	Endpoint	Study 26[a]	Study 12[b]		Study1403740[c]		
		ATX-101 2 mg/cm^2	Placebo	ATX-101 All Doses	Placebo	ATX-101 1 mg/cm^2	ATX-101 2 mg/cm^2
1 year	**CR-SMFRS** %	90.4%	82.4%	93.9%	95.5%	85.0%	87.0%
	1-grade (n/N)	(113/125)	(14/17)	(77/82)	(21/22)	(34/40)	(47/54)
	PR-SMFRS %	80.7%	94.4%	84.2%	82.1%	80.0%	90.7%
	1-grade (n/N)	(96/119)	(17/18)	(32/38)	(23/28)	(32/40)	(49/54)
	Composite %	83.5%	71.4%	78.6%	87.5%	75.9%	88.3%
	1-grade (n/N)	(86/103)	(5/7)	(22/28)	(14/16)	(22/29)	(38/43)
2 years	**CR-SMFRS** %	NA	75.0%	91.7%	86.4%	90.0%	87.0%
	1-grade (n/N)		(12/16)	(66/72)	(19/22)	(36/40)	(47/54)
	PR-SMFRS %	NA	82.4%	90.3%	81.5%	77.5%	88.9%
	1-grade (n/N)		(14/17)	(28/31)	(22/27)	(31/40)	(48/54)
	Composite %	NA	83.3%	81.1%	80.0%	69.0%	81.4%
	1-grade (n/N)		(5/6)	(18/22)	(12/15)	(20/29)	(35/43)
3 years	**CR-SMFRS** %	NA	66.7%	80.4%	NA	NA	NA
	1-grade (n/N)		(6/9)	(41/51)			
4 years	**CR-SMFRS** %	NA	20.0%	87.9%	NA	NA	NA
	1-grade (n/N)		(1/5)	(29/33)			

[a] Study 26 followed patients for 1 year after last treatment.
[b] Study 12 includes patients from Phase 2 Studies 03, 07 and 15. Studies 03 and 07 did not include the PR-SMFRS, therefore Study 12 PR-SMFRS and Composite SMFRS data are based on patients from Study 15.
[c] Study 1403740 followed patients from EU Phase 3 Studies 16 and 17 for 2 years.
Source: Studies 12, 26, and 1403740 clinical study reports

4.5. Efficacy Conclusion

The clinical development program for ATX-101 was comprehensive. The studies included patient populations relevant to the individual study objectives and representative of patients in the general population with undesired SMF and who would be candidates for treatment with ATX-101. Throughout the ATX-101 clinical program, and particularly in the Phase 3 studies, efficacy endpoints were rigorously collected and analyzed using appropriate, prespecified statistical methods. Across studies, the efficacy results consistently demonstrate the superiority of ATX-101 relative to placebo in the reduction of SMF. In particular, the results of the 2 pivotal Phase 3 studies are similar to one another, as were the results of the 2 supportive EU Phase 3 studies. Although in many cases the pivotal Phase 3 and supportive Phase 2 and 3 studies used different efficacy endpoints and study designs, the results are consistently clear and positive in favor of ATX-101. When data collected in the supportive studies were analyzed using methods comparable to those used in the pivotal Phase 3 studies, ATX-101 was consistently shown to

improve the appearance of moderate to severe convexity or fullness associated with SMF in adults.

In conclusion, efficacy of ATX-101 has been demonstrated by individual and combined clinical study results from a comprehensive clinical program. In particular, the 2 adequate and well-controlled pivotal studies met their co-primary and secondary endpoints and demonstrated that ATX-101, when administered at the recommended dose of 2 mg/cm^2 for up to 6 treatments at 4-week intervals, was superior to placebo in the reduction of SMF, as assessed by the clinician (CR-SMFRS), the patient (PR-SMFRS, PR-SMFIS, etc.), and objective measurements (MRI and calipers). Consistent and long-lasting improvements in SMF were documented across studies in the clinical program and these observable improvements had a positive impact on patient self-perceptions and led to a high degree of patient satisfaction. Results of the clinical studies completed to date indicate that ATX-101 is effective for the proposed indication and represents a promising nonsurgical and less invasive alternative to liposuction and excisional or reconstructive surgery for reduction of SMF.

5. OVERVIEW OF SAFETY

5.1. Exposure to ATX-101 in the Overall Clinical Development Program

The safety of ATX-101 was evaluated in 23 Phase 1 to Phase 3 clinical studies, 19 of which support the SMF indication (Figure 1). Of the 19 SMF studies, 16 are included in the integrated safety dataset:

- 2 pivotal Phase 3 studies (Studies 22 and 23, N = 1019)
- 2 supportive Phase 3 studies (Studies 16 and 17, N = 716)
- 3 Phase 2 studies (Studies 03, 07, and 15, N = 284)
- 5 Phase 1 studies (Studies 08, 19, 24, 30, and 32, N = 295)
- 4 LTFU studies (nontreatment Study 12, N = 203 [subset of patients treated in Studies 03, 07 and 15], nontreatment Study 1403740, N = 201 [subset of patients treated in Studies 16 and 17], nontreatment Study 35, N = 224 [subset of patients treated in the pivotal Studies 22 and 23], and open-label treatment and LTFU Study 26, N = 165)

The other 3 studies contributing to the safety database are Phase 3B Studies 27 and 28 that are ongoing and blinded, and recently completed Phase 3B Study 36. Individual safety summaries from these studies were presented in the 120-Day Safety Update and Study 36 patients are included in the updated exposure numbers herein (Table 20).

Of the 2664 patients participating in the 18 completed treatment studies, 1698 were treated with ATX-101, 911 were treated with placebo, and 55 were treated with active control (for evaluation of QT interval prolongation in Study 24). Over 700 patients have been exposed to up to 6 monthly treatments with ATX-101 at the 2 mg/cm^2 dosage intended for clinical use (see Studies 22, 23, 26 and 15 in Table 20).

For the purpose of overall safety evaluations, the safety population included all patients who received at least 1 dose of study drug (ATX-101, placebo, or active control). All patients were analyzed according to the treatment actually received, regardless of randomized treatment assignment.

Table 20: Number of Patients Exposed to ATX-101 by Dose

Studies With Doses Expressed as Area-adjusted Dose of ATX-101

Indication Phase	Study No.	No. of Treatment Sessions	ATX-101-treated Patients 1 mg/cm²	2 mg/cm²	4 mg/cm²	8 mg/cm²	Total	Placebo/ Control-treated Patients	Total
SMF Phase 3/3B	Study 22[a]	Up to 6	---	257	---	---	257[a]	248	505
	Study 23[b]	Up to 6	---	258	---	---	258[b]	256	514
	Study 16	Up to 4	119	121	---	---	240	122	362
	Study 17	Up to 4	118	122	---	---	240	114	354
	Study 26	Up to 6	---	165	---	---	165	---	165
	Study 36	1		68			68	15	83
	Subtotal		237	991	---	---	1228	755	1983
SMF Phase 2	Study 03	Up to 4	20	20	22	---	62	22	84
	Study 07	Up to 4	---	13	44	---	57	14	71
	Study 15	Up to 6	41	43	---	---	84	45	129
	Subtotal		61	76	66	0	203	81	284
SMF Phase 1 & single-dose studies	Study 08	1	3	3	9	9	24	---	24
	Study 19	1	---	24	---	---	24	---	24
	Study 24[c]	1	---	---	55	54	109	109[c]	218
	Study 30[d]	1	---	---	5	---	5	---	5
	Study 32	1	---	24	---	---	24	---	24
	Subtotal		3	51	69	63	186	109	295
	Total		301	1118	135	63	1617	945	2562

Studies in Which ATX-101 Was Administered Into SC Abdominal Fat

Indication Phase	Study No.	No. of Treatment Sessions	ATX-101-treated Patients 1 mg/cm²	2 mg/cm²	4 mg/cm²	8 mg/cm²	Total	Placebo/ Control-treated Patients	Total
SC Fat Phase 1	Study 10[e]	1 or 2	---	---	---	---	14	---	14
	Study 18[f]	1	---	10	---	---	10	---	10
	Subtotal			10			24		24

Studies With Doses Expressed as Concentration (mg/mL) of ATX-101 (Lipoma)

Indication Phase	Study No.	No. of Treatment Sessions	ATX-101-treated Patients 5 mg/mL	10 mg/mL	20 mg/mL	40 mg/mL	Total	Placebo Patients	Total
Lipoma Phase 1-2	Study 04	2	3	3	3	3	12	4	16
	Study 05	4	0	15	15	15	45	17	62
	Subtotal		3	18	18	18	57	21	78

ATX-101 = deoxycholic acid injection; No. = number; SC = subcutaneous; SMF = submental fat

[a] The values for numbers of patients for Study 22 reflect the inclusion of Patient 124-009 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 4, when ATX-101 was administered in error.

[b] The values for numbers of patients for Study 23 reflect the inclusion of Patient 533-006 in the ATX-101 treatment group. This patient was randomized to the placebo group and received placebo treatment at all treatment sessions except Visit 4, when ATX-101 was administered in error.

[c] In Study 24, 55 patients were dosed with 400 mg moxifloxacin, an active comparator, and 54 were dosed with placebo.

[d] Single session for treatment of SMF and single session for treatment of SC abdominal fat.

[e] In Study 10, treatment was given into SC abdominal fat. Each patient received all doses of ATX-101 and placebo as a control. Patients from this study are not counted in the individual concentration groups.

[f] In Study 18, treatment was given into SC abdominal fat.

Source: Integrated Summary of Safety Posttext Table 1.1 in NDA 206333 and clinical study reports for Studies 03, 04, 05, 07, 08, 10, 18, 24, 30, and 36

5.2. Exposure to ATX-101 in the Pivotal Studies

The safety population for the randomized, double-blind, placebo controlled pivotal Phase 3 Studies 22 and 23 included all patients who received at least 1 dose of study drug (ATX-101 or placebo) and all patients were analyzed according to the treatment actually received, regardless of randomized treatment assignment. The pivotal studies pooling group consists of all patients treated in Studies 22 and 23, which were conducted according to identical protocols in the US and Canada. The AE profiles from the individual pivotal Phase 3 studies were comparable, supporting the use of the pooled pivotal data to draw safety conclusions regarding ATX-101 when used for improvement in the appearance of convexity/fullness associated with SMF. Safety data across all SMF studies were also consistent with data from the pivotal studies and are discussed as appropriate.

Table 21 summarizes exposure to ATX-101 in the pivotal studies. Most patients (81.2%) in the placebo group received the maximum number of treatment sessions (6), whereas a substantially lower percentage of patients (59.0%) in the ATX-101 group underwent 6 treatments. The average number of treatments was 4.7 for ATX-101 and 5.4 for placebo. Consistent with these observations, the median total volume of study drug injected over the course of treatment was also lower in the ATX-101 group (24.2 mL) than in the placebo group (33.6 mL). The median total amount of DCA received by the ATX-101 group was 242.0 mg, which is substantially lower than the maximum amount allowed over the course of 6 treatments (600 mg). To adjust for differences in numbers of treatments, the average volume of study drug injected per treatment was calculated for each patient, and the median volume per treatment appeared to be slightly lower in the ATX-101 group (5.4 mL) compared to the placebo group (6.1 mL). The volume per treatment session in both treatment groups was considerably lower than the maximum allowed per protocol (ie, 10 mL).

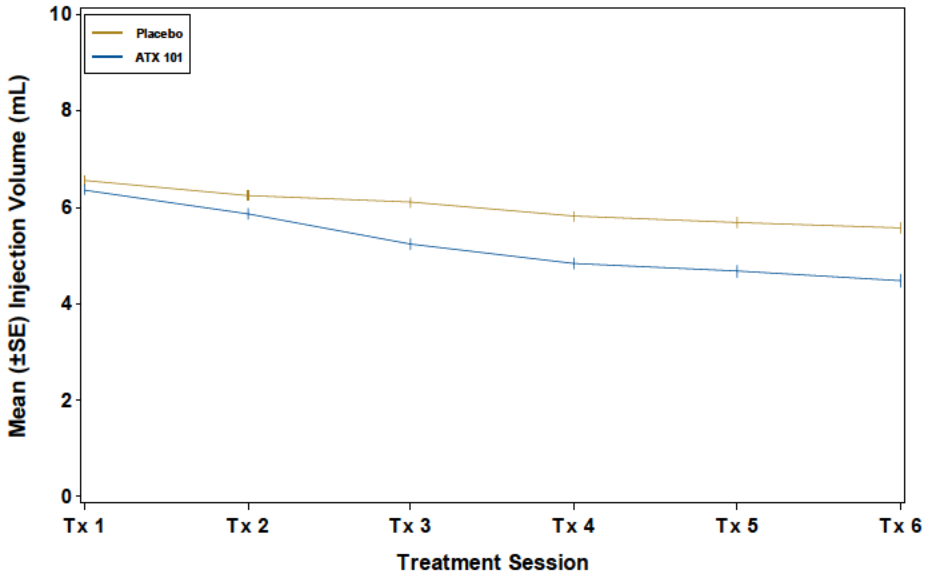
The volume of study drug (and corresponding number of injections administered) tended to decrease with subsequent treatment sessions, particularly in the ATX-101 group (Figure 20). This finding is consistent with greater reductions in SMF over time in the ATX-101 group than the placebo group.

Table 21: Exposure to Study Drug across All Treatment Sessions—Pivotal Studies

Variable	Placebo N = 506[a]	ATX-101 2 mg/cm^2 N = 515
Total number of treatment sessions, n (%)		
1	17 (3.4)	61 (11.8)
2	21 (4.2)	29 (5.6)
3	17 (3.4)	33 (6.4)
4	20 (4.0)	48 (9.3)
5	20 (4.0)	40 (7.8)
6	411 (81.2) [a]	304 (59.0)
Total volume (mL) of study drug received		
Mean	32.8	25.3
SD	14.05	14.01
Median	33.6	24.2
Range (min, max)	(3, 60)	(0.8, 60)
Total amount of DCA received (mg)		
Mean	0.0	252.9
SD	0.00	140.10
Median	0.0	242.0
Range (min, max)	(0, 0)	(8, 600)
Average volume of study drug received per treatment session (mL)		
Mean	6.0	5.4
SD	2.06	2.05
Median	6.1	5.4
Range (min, max)	(1.0, 10.0)	(40.8, 10.0)

[a] Exposure calculations considered all actual treatments; therefore, 2 placebo patients inadvertently treated with ATX-101 in one treatment session are counted in both treatment groups for exposure purposes only.
ATX-101 = deoxycholic acid injection; max = maximum; min = minimum; SD = standard deviation
Note: Study drug exposure (mg) = total injection volume (mL) x drug concentration (mg/mL).
Source: Integrated Summary of Safety Table 9 in NDA 206333

Figure 20: Mean (SE) Volume of Study Drug Injected at Each Treatment Session



Source: Integrated Summary of Safety Posttext Table 4.1.1 in NDA 206333

5.3. Adverse Events

5.3.1. Overview of Adverse Events

The overall AE experience presents a consistent and acceptable safety profile when ATX-101 is used for the improvement in the appearance of submental convexity or fullness associated with SMF. Table 22 presents an overview of AEs reported in the pivotal studies. As expected for a facial injectable product, AEs associated with treatment were reported in most patients in both treatment groups (97.3% ATX-101; 89.7% placebo) and were predominantly local reactions in the treatment area (reported in 94.6% of patients treated with ATX-101 and 77.4% of patients treated with placebo). These AEs were usually transient and resolved within the treatment interval; 82% of AEs in the ATX-101 group and 89% of AEs in the placebo group resolved within 30 days. Most AEs were mild or moderate in severity (98% of events in ATX-101 patients; 99% of events in placebo patients), and typically required no action to be taken for the event to resolve (88% of events in ATX-101 patients; 85% of events in placebo patients). Adverse events not associated with the treatment area, including systemic events, and judged to be related to study drug were uncommon and typically not serious or severe. In the pivotal studies, SAEs were reported in 2.5% of patients treated with ATX-101 and 4.4% of patients treated with placebo. No SAEs were reported to be related to study drug.

Table 22: Overview of Adverse Events—Pivotal Studies

Category Variable	Placebo N = 504 n (%)	ATX-101 2 mg/cm^2 N = 515 n (%)
Any AE		
Patients	452 (89.7)	501 (97.3)
Events	3156 (100.0)	5538 (100.0)
AEs related to study drug		
Patients	390 (77.4)	487 (94.6)
Events	2131 (67.5)	4549 (82.1)
SAEs		
Patients	22 (4.4)	13 (2.5)
Events	25 (0.8)	21 (0.4)
Study-drug-related SAEs		
Patients	0	0
Events	0	0
AEs associated with treatment area		
Patients	411 (81.5)	494 (95.9)
Events	2320 (73.5)	4710 (85.0)
AEs not associated with treatment area		
Patients	295 (58.5)	289 (56.1)
Events	836 (26.5)	828 (15.0)
AE severity		
Mild AEs		
Patients	266 (52.8)	200 (38.8)
Events	2807 (88.9)	4479 (80.9)
Moderate AEs		
Patients	170 (33.7)	246 (47.8)
Events	328 (10.4)	969 (17.5)
Severe AEs		
Patients	16 (3.2)	55 (10.7)
Events	21 (0.7)	90 (1.6)
AE outcome		
Recovered/resolved		
Patients	443 (87.9)	500 (97.1)
Events	3015 (95.5)	5371 (97.0)
Recovering/resolving		
Patients	24 (4.8)	37 (7.2)
Events	29 (0.9)	51 (0.9)
Not recovered/not resolved		
Patients	33 (6.5)	42 (8.2)
Events	39 (1.2)	52 (0.9)
Fatal		
Patients	1 (0.2)	1 (0.2)
Events	1 (<0.1)	1 (<0.1)
Unknown		
Patients	44 (8.7)	35 (6.8)
Events	72 (2.3)	63 (1.1)
Action taken		
No action taken		
Patients	223 (44.2)	233 (45.2)
Events	2677 (84.8)	4865 (87.8)

Category Variable	Placebo N = 504 n (%)	ATX-101 2 mg/cm^2 N = 515 n (%)
Action taken		
Patients	229 (45.4)	268 (52.0)
Events	479 (15.2)	673 (12.2)
AEs resulting in fewer than the maximum number of treatments		
Patients	7 (1.4)	35 (6.8)
Events	8 (0.3)	46 (0.8)
AEs that led to discontinuation from study		
Patients	4 (0.8)	16 (3.1)
Events	4 (0.1)	26 (0.5)
AE duration		
1-3 days		
Patients	300 (59.5)	334 (64.9)
Events	980 (31.1)	1107 (20.0)
4-7 days		
Patients	291 (57.7)	378 (73.4)
Events	718 (22.8)	1133 (20.5)
8-14 days		
Patients	330 (65.5)	387 (75.1)
Events	878 (27.8)	1405 (25.4)
15-30 days[a]		
Patients	144 (28.6)	334 (64.9)
Events	243 (7.7)	918 (16.6)
31-60 days		
Patients	71 (14.1)	220 (42.7)
Events	109 (3.5)	393 (7.1)
61-90 days		
Patients	29 (5.8)	124 (24.1)
Events	40 (1.3)	168 (3.0)
91-180 days		
Patients	30 (6.0)	134 (26.0)
Events	35 (1.1)	185 (3.3)
> 180 days		
Patients	13 (2.6)	54 (10.5)
Events	13 (0.4)	63 (1.1)
Ongoing		
Patients	93 (18.5)	106 (20.6)
Events	140 (4.4)	166 (3.0)

AE = adverse event; ATX-101 = deoxycholic acid injection; CRF = case report form; SAE = serious adverse event

[a] The percentage of events with a duration ≤ 30 days was 82.4% (4563/5553) in the ATX-101 group and 89.3% (2819/3156) in the placebo group.

Notes: Event counts and percentages included all events, including multiple events per patient. Study-drug-related AEs included those events with relationship equal to related or missing. Adverse events associated with the treatment area included events: (1) identified on a prespecified preferred term list (2) identified as associated with the treatment area on the CRF. Patients were counted once for the maximum severity of event experienced or maximum action taken. Patients were counted once per level for the following: treatment area association, event outcome, and event duration. As such, the percentage of patients may sum to greater than 100% in these sections. Action taken included concomitant medication, concomitant procedure, study discontinuation, and other action.

Source: Integrated Summary of Safety Table 30 in NDA 206333

5.3.2. Incidence of Adverse Events

Table 23 summarizes the incidence of the AEs occurring in the pivotal studies in ≥ 2% of patients in the ATX-101 treatment group by preferred term. Overall, the types and incidences of AEs across all SMF studies were similar to that described for the pivotal studies group.

The most common preferred terms of AEs reported by patients in both the ATX-101 and placebo groups were injection site hematoma (> 99% of which was bruising), injection site pain, injection site anesthesia, injection site edema, injection site swelling, injection site erythema, injection site paresthesia, injection site induration, injection site nodule, and injection site pruritus. In general, all of these events were observed more frequently in the ATX-101 group with the exception of injection site hematoma/bruising, which was similar in both groups and likely related to the needle injection procedure.

Table 23: Most Common (Frequency ≥ 2% in ATX-101 Group) Preferred Terms of Adverse Events - Pivotal Studies

Preferred Term Statistic	Placebo N = 504 n (%)	ATX-101 (2 mg/cm^2) N = 515 n (%)
Injection site hematoma (bruising)	353 (70.0)	368 (71.5)
Injection site pain	158 (31.3)	358 (69.5)
Injection site anesthesia	29 (5.8)	341 (66.2)
Injection site edema	147 (29.2)	311 (60.4)
Injection site swelling	79 (15.7)	171 (33.2)
Injection site erythema	90 (17.9)	137 (26.6)
Injection site induration	13 (2.6)	120 (23.3)
Injection site paresthesia	19 (3.8)	71 (13.8)
Injection site nodule	13 (2.6)	69 (13.4)
Injection site pruritus	30 (6.0)	64 (12.4)
Headache	19 (3.8)	42 (8.2)
Nasopharyngitis	39 (7.7)	35 (6.8)
Skin tightness	6 (1.2)	24 (4.7)
Injection site warmth	8 (1.6)	22 (4.3)
Nerve injury	2 (0.4)	22 (4.3)
Blood glucose increased	18 (3.6)	18 (3.5)
Upper respiratory tract infection	30 (6.0)	17 (3.3)
Sinusitis	21 (4.2)	17 (3.3)
Tri-iodothyronine decreased	14 (2.8)	16 (3.1)
Influenza	20 (4.0)	15 (2.9)
Oropharyngeal pain	7 (1.4)	15 (2.9)
Urinary tract infection	7 (1.4)	14 (2.7)
Hypertension	7 (1.4)	13 (2.5)
Nausea	3 (0.6)	12 (2.3)
Protein urine	14 (2.8)	11 (2.1)
Dysphagia	1 (0.2)	10 (1.9[a])

ATX-101 = deoxycholic acid injection
[a] Dysphagia is included due to its status as an AE of special interest and frequency only slightly less than 2%
Notes: Patients experiencing more than 1 AE for a preferred term were counted only once for that preferred term. Preferred terms are displayed in decreasing order of frequency in the ATX-101 group and were based on MedDRA Version 14.1.
Source: Integrated Summary of Safety Posttext Table 6.4.1.1 in NDA 206333

5.3.3. Adverse Events Associated With the Treatment Area

The majority of all AEs (85.0% of ATX-101 events; 73.5% of placebo events) were associated with the treatment area. Since the treatment-area-associated events were the most commonly reported events, the overall congruence between the incidence of all AEs and that of AEs related to study drug is substantial for all observations.

Adverse events not associated with the treatment area, including systemic events, were uncommon, typically not serious or severe, tended to be distributed among a range of SOCs and did not exhibit a pattern that would indicate the existence of a relationship with ATX-101.

5.3.4. Duration of Adverse Events

Most AEs resolved within 1 treatment interval, having median durations of ≤ 30 days (82% of events in the ATX-101 group and 89% of events in the placebo group; Table 22). The median duration of any AE was 18 days for ATX-101 patients and 9 days for placebo patients.

The majority of common injection site AEs in the ATX-101 group (ie, bruising, pain, anesthesia, edema, swelling, erythema, induration, paresthesia, nodule, pruritus) had median durations of ≤ 30 days. The range of median durations for these events in the ATX-101 group was 7 to 43 days, compared with 2 to 6 days in the placebo group. Injection site nodule, injection site induration and injection site numbness had the longest median durations: 23, 28 and 43 days, respectively. The maximum duration observed for any of these common injection site AEs was 349 days (anesthesia/numbness); however, it was uncommon for events to exceed 180 days. As can be seen across all AEs (Table 22), 1.1% of events in ATX-101 patients and 0.4% of events in placebo patients had durations longer than 180 days.

5.3.5. Adverse Event Severity

For the majority of patients in the pivotal studies, regardless of treatment, the maximum severity of AEs experienced at least once by a patient over the course of multiple treatment sessions was mild or moderate (86.6% of ATX-101 patients; 86.5% of placebo patients). In addition, most of the events in both treatment groups were either mild or moderate (98.4% of ATX-101 events; 99.3% of placebo events) (Table 22).

Severe AEs were reported by 10.7% of patients in the ATX-101 group and 3.2% of patients in the placebo group. The severe event frequencies were 1.6% of ATX-101 events and 0.7% of placebo events. The most common severe AEs reported by patients in the ATX-101 group were injection site pain (3.9% ATX-101; 0.2% placebo), injection site edema (3.3% ATX-101; 0 placebo), injection site hematoma (0.8% ATX-101; 0.2% placebo), and injection site swelling (0.8% ATX-101; 0 placebo). Other preferred terms of severe AEs were reported by ≤ 2 patients each in either treatment group.

5.3.6. Adverse Events by Treatment Session

An overview of AEs by treatment session in the pivotal studies is presented in Table 24. In the ATX-101 treatment group, the percentage of patients reporting any AE was highest during the first session (486/514 patients treated, 94.6%) and decreased in subsequent sessions to reach its lowest value at Session 5 (266/344 patients treated, 77.3%). In the placebo group, the percentage of patients reporting any AE also decreased over sessions, but the decrease was not as

pronounced as in the ATX-101 group, falling from 69.7% (352/505 patients treated) at Session 1 to 57.3% (247/431 patients treated) at Session 5. These data support the observation that AEs due to treatment with ATX-101 have the highest incidence at the start of treatment and occur less frequently as treatment progresses.

Table 24: Overview of Adverse Events by Treatment Session—Pivotal Studies

	Placebo N = 504			ATX-101 2 mg/cm^2 N = 515		
Treatment Session	Patients Who Received Treatment n (%)	Patients With Events n (%)	Number of Events	Patients Who Received Treatment n (%)	Patients With Events n (%)	Number of Events
Session 1	505 (100.0)	352 (69.8)	667	514 (99.8)	486 (94.4)	1791
Session 2	489 (97.0)	302 (59.9)	575	454 (88.2)	394 (76.5)	1025
Session 3	467 (92.7)	274 (54.4)	489	426 (82.7)	350 (68.0)	835
Session 4	452 (89.7)	268 (53.2)	473	392 (76.1)	312 (60.6)	695
Session 5	431 (85.5)	247 (49.0)	414	344 (66.8)	266 (51.7)	599
Session 6	412 (81.7)	270 (53.6)	538	304 (59.0)	239 (46.4)	593

Events were assigned to treatment sessions based on a comparison of event start date and treatment session study drug administration dates. Percentages of patients with events are calculated based on all patients treated on study (515 ATX-101; 504 placebo).
Source: Integrated Summary of Safety Table 52 in NDA 206333

The incidence and severity across treatment sessions was also evaluated for specific common treatment area AEs (ie, bruising, pain, anesthesia, and swelling).

Injection Site Bruising: At the first treatment session, 289 ATX-101 patients (56.1%) and 226 placebo patients (44.8%) reported bruising. The percentage of ATX-101 patients reporting bruising declined over subsequent sessions, from 43.9% at Session 2 to 26.9% at Session 6. Moderate or severe bruising was reported most frequently in the first session, and diminished over subsequent sessions.

Injection Site Pain: At the first treatment session, 302 ATX-101 patients (58.6%) and 99 placebo patients (19.6%) reported injection site pain. The percentage of ATX-101 patients reporting injection site pain declined over subsequent sessions, from 34.9% at Session 2 to 19.3% at Session 6. As with the AEs discussed above, the percentage of patients reporting moderate or severe injection site pain was greatest in the first session.

Injection Site Anesthesia (Numbness): At the first treatment session, 320 ATX-101 patients (62.1%) and 29 placebo patients (5.8%) reported numbness. The percentage of ATX-101 patients reporting numbness declined over subsequent sessions, from 22.4% at Session 2 to 8.9% at Session 6. The percentage of patients reporting moderate or severe numbness was greatest in the first session.

Injection Site Swelling: At the first treatment session, 402 ATX-101 patients (78.1%) and 142 placebo patients (28.2%) reported injection site swelling events. The percentage of ATX-101 patients reporting injection site swelling declined over subsequent sessions, from 58.3% at

Session 2 to 47.9% at Session 6. Similarly, the percentage of patients reporting moderate or severe swelling was greatest in the first session and tended to diminish over subsequent sessions.

5.3.7. Serious Adverse Events

The incidence of SAEs in the pivotal studies was low and generally similar between the ATX-101 and placebo groups (Table 25). Thirteen (2.5%) patients in the ATX-101 group and 22 (4.4%) patients in the placebo group reported SAEs. The total numbers of events were 21 and 25, respectively. Except for breast cancer and diverticulitis, all preferred terms of SAEs were reported by 1 patient each. Breast cancer and diverticulitis were reported by 2 patients each in the placebo group. No SAE in the pivotal studies was considered related to study drug.

The incidence of SAEs was also evaluated for patients in the broader population of all SMF studies in the clinical development program. No SAEs occurred in > 1 patient in the 2 mg/cm^2 ATX-101 treatment group. The only SAEs reported in > 1 patient in the placebo group were breast cancer, diverticulitis, and osteoarthritis (2 patients each). Consistent with the pivotal studies, few patients experienced SAEs and only 1 SAE in the whole program (Study 17, injection site nerve damage) was considered to be related to study drug. This event was moderate in severity and recorded as a suspected, unexpected, serious adverse reaction (SUSAR) because nerve injury was not yet specified as an expected event in the investigator brochure and because it was unknown at the time if the event would resolve, which it did. Nerve injury events are discussed in further detail in Section 5.3.11.1.

Table 25: Serious Adverse Events by System Organ Class and Preferred Term—Pivotal Studies

System Organ Class Preferred Term	Placebo N = 504 n (%)	ATX-101 2 mg/cm^2 N = 515 n (%)
Patients With Any AE	22 (4.4)	13 (2.5)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	3 (0.6)	3 (0.6)
Breast Cancer Recurrent	0	1 (0.2)
Ovarian Cancer	0	1 (0.2)
Uterine Cancer	0	1 (0.2)
Uterine Leiomyoma	0	1 (0.2)
Breast Cancer	2 (0.4)	0
Multiple Myeloma	1 (0.2)	0
Gastrointestinal Disorders	3 (0.6)	2 (0.4)
Colitis Microscopic	0	1 (0.2)
Gastrooesophageal Reflux Disease	1 (0.2)	1 (0.2)
Gastrointestinal Haemorrhage	1 (0.2)	0
Hiatus Hernia	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Infections and Infestations	5 (1.0)	2 (0.4)
Abdominal Abscess	0	1 (0.2)
Urinary Tract Infection	0	1 (0.2)
Abscess Oral	1 (0.2)	0
Diverticulitis	2 (0.4)	0
Influenza	1 (0.2)	0
Spinal Cord Infection	1 (0.2)	0
Injury, Poisoning and Procedural Complications	2 (0.4)	2 (0.4)
Concussion	0	1 (0.2)
Contusion	0	1 (0.2)
Head Injury	0	1 (0.2)
Road Traffic Accident	0	1 (0.2)
Skull Fracture	0	1 (0.2)
Humerus Fracture	1 (0.2)	0
Toxicity To Various Agents	1 (0.2)	0
Musculoskeletal and Connective Tissue Disorders	2 (0.4)	2 (0.4)
Osteoarthritis	1 (0.2)	1 (0.2)
Spinal Column Stenosis	0	1 (0.2)
Intervertebral Disc Protrusion	1 (0.2)	0
Nervous System Disorders	1 (0.2)	1 (0.2)
Meningism	0	1 (0.2)
Transient Ischaemic Attack	1 (0.2)	0
Reproductive System and Breast Disorders	0	1 (0.2)
Cystocele	0	1 (0.2)
Rectocele	0	1 (0.2)
Uterine Prolapse	0	1 (0.2)

System Organ Class Preferred Term	Placebo N = 504 n (%)	ATX-101 2 mg/cm^2 N = 515 n (%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	1 (0.2)
Respiratory Failure	0	1 (0.2)
Respiratory Distress	1 (0.2)	0
Surgical and Medical Procedures	3 (0.6)	1 (0.2)
Intervertebral Disc Operation	0	1 (0.2)
Hip Arthroplasty	1 (0.2)	0
Hip Surgery	1 (0.2)	0
Vaginal Operation	1 (0.2)	0
Cardiac Disorders	2 (0.4)	0
Cardiac Arrest	1 (0.2)	0
Cardiac Failure Congestive	1 (0.2)	0
Metabolism and Nutrition Disorders	1 (0.2)	0
Dehydration	1 (0.2)	0
Renal and Urinary Disorders	1 (0.2)	0
Urethral Disorder	1 (0.2)	0

AE = adverse event; ATX-101 = deoxycholic acid injection; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Notes: Patients experiencing more than 1 SAE within a preferred term or system organ class and/or preferred term were counted only once for that system organ class/preferred term. Incidences are displayed in descending order of incidence of system organ class and by preferred term within system organ class. System organ class and preferred term were based on MedDRA Version 14.1.
Source: Integrated Summary of Safety Table 56 in NDA 206333

5.3.8. Deaths

There were 2 reported deaths in the pivotal studies (road traffic accident in a patient treated with ATX-101 and heroin toxicity in a patient treated with placebo [preferred term = toxicity to various agents]). There were an additional 2 deaths in the overall ATX-101 SMF development program: cardiac arrest and cardiac death, both of which occurred in patients who received 2 mg/cm^2 ATX-101. No death was considered by the investigator to be related to study drug. The 2 cardiac deaths occurred > 140 days after the last treatment.

5.3.9. Adverse Events Resulting in Fewer Than the Maximum Number of Treatment Sessions

The majority of patients in the ATX-101 group who received fewer than the maximum number of treatments due to an AE did so because of an AE in the General Disorders and Administration Site Conditions SOC (26 patients [5.0%]). The most common (patient incidence ≥ 1.0%) preferred terms in the ATX-101 group were injection site pain (11 patients [2.1%]), injection site anesthesia (8 patients [1.6%]), and injection site edema (5 patients [1.0%]). In the placebo group, no AE leading to fewer than the maximum number of treatments occurred in > 1 patient. Other reasons for patients not receiving the maximum number of treatment sessions, such as insufficient remaining SMF for safe administration of study drug, or patient satisfaction with SMF reduction, are discussed in Section 4.2.4.2.

5.3.10. Adverse Events Leading to Discontinuation From Study

As shown in Table 22, 16 patients (3.1%) in the ATX-101 group and 4 patients (0.8%) in the placebo group discontinued from study due to AEs. Injection site pain was the most common event leading to discontinuation from study, occurring in 5 patients (1.0%) in the ATX-101 group and no patients in the placebo group. Injection site anesthesia and injection site edema each resulted in early discontinuation from study for 4 patients (0.8%) in the ATX-101 group and no patients in the placebo group. No other AE resulted in early study discontinuation in > 2 patients in either treatment group.

5.3.11. Adverse Events of Special Interest

Adverse events of special interest were prespecified based on events observed in earlier studies and these AESIs grouped together similar preferred terms (ie, those describing similar events, for example swelling and edema) to better identify and characterize common AEs/reactions. Most of the AESIs have been adequately characterized based on AE reports presented earlier in Section 5.3. Of note, motor nerve injury and ulceration were identified as special interest AEs likely to be related to incorrect injection procedure or technique; either injection placement outside of the submental region or failure to inject midlevel into SC fat. These 2 AESI categories are further discussed below, along with dysphagia, which was observed in 1.9% of patients treated with ATX-101 in the pivotal studies and was not previously characterized.

5.3.11.1. Injection Site Motor Nerve Injury

This category describes events consistent with motor neuropraxia (presenting as an asymmetrical smile), suggesting irritation or injury of the marginal mandibular branch of the facial nerve. The marginal mandibular branch of the facial nerve courses outside of the SMF region but is adjacent to the external border of the potential treatment area (within a 3-cm radius circle centered at a point approximately 2 cm lateral to and 2 cm inferior to the oral commissure).

In the pivotal studies, injection site nerve injury was reported in 22 patients (4.3%; 23 events) in the ATX-101 group and 2 patients (0.4%; 2 events) in the placebo group. Most events were mild or moderate in severity, with 1 patient (0.2%) in the ATX-101 group and no patients in the placebo group reporting severe events. The 1 severe event was reported at the first treatment session in a 57-year-old female. This event resolved without sequelae and the patient went on to receive 3 additional treatments, stopping treatment after Session 4 due to therapeutic success.

The median duration of nerve injury events in the pivotal studies was 42 days (maximum 298 days) in the ATX-101 group and 85 days (maximum 115 days) in the placebo group. All of these nerve injury events recovered/resolved without sequelae. At the first treatment session, 9 ATX-101 patients (1.7%) and no placebo patients reported injection site nerve injury. The percentage of ATX-101 patients reporting this category of event declined over subsequent sessions, from 1.5% at Session 2 to 0.3% at Session 6.

In the broader safety population of all SMF studies in the development program, there were 39 events of injection site nerve injury reported in 30 patients (2.9%) in the ATX-101 2 mg/cm^2 group and 3 events reported in 3 patients (0.3%) in the placebo group. Of note, the attempt to capture any potential motor nerve injury event resulted in the inclusion of 4 patients who did not have nerve injury events related to the region of interest, ie, the marginal mandibular nerve (3

pinched nerves [2 ATX-101 2 mg/cm^2 and 1 placebo] and 1 report of thumb weakness in a patient treated with ATX-101 at >2 mg/cm^2).

There was 1 nerve injury SAE (initially reported as a SUSAR; see Section 5.3.7). This event was graded as moderate and judged to be related to study drug; severity was reduced to mild after 38 days and the nerve injury resolved after a total of 57 days. There was also 1 severe nerve injury event reported in the 2 mg/cm^2 group, which resolved without sequelae after 85 days. The duration of nerve injury events in the ATX-101 treatment group ranged from a few days to > 180 days, with the majority of events having a duration of ≤ 60 days. Only 3 ATX-101 patients had nerve injury events with a duration > 90 days: Subject 22-112-007 (298 days; the event did not result in fewer than the maximum number of treatments, the patient completed the study, and the event resolved without sequelae), Subject 22-137-010 (114 days; the patient received 1 treatment and left the study due to administrative reasons; the event resolved without sequelae), and Subject 26-009-005 (115 days; the AE occurred after the fifth treatment and the patient discontinued treatment due to the AE, but completed the study; the event resolved without sequelae).

To reduce the potential for motor neuropraxia of the marginal mandibular nerve, injection above the inferior aspect of the mandible, or within the region defined by a 3-cm radius circle described above, is not advised. General guidance on the risk of nerve injury was given to investigators involved in the pivotal studies, and more specific guidance based on continued learnings over the course of the development program (including relevant anatomy and measurements to identify the region of concern) is planned to be provided in the product labeling and in physician training materials.

5.3.11.2. Skin Ulceration

This category describes small (typically 3-5 mm) superficial erosions of the skin/dermis at injection sites within the treatment area. These events are consistent with either shallow injections superficial to the SC fat (ie, into the skin/dermis) or continued injection during needle withdrawal.

The only treatment area skin ulceration (erosion) event observed in the pivotal studies (and across all of the placebo-controlled SMF studies) occurred in a 53-year-old male in Study 23 during his last treatment session. The event lasted 23 days and resolved without sequelae. Two patients in the placebo-controlled studies (1 each for ATX-101 and placebo) had ulceration events unrelated to treatment or the region of interest (both gluteal lesions). In open-label Phase 3B Study 26, 4 study-drug-related events of superficial injection site skin ulceration were reported (in addition to 1 event unrelated to study drug). The 4 events were mild or moderate, had durations of 13 to 26 days and also resolved without sequelae.

Across the SMF development program, the overall incidence of study-drug-related skin ulcerations in patients treated with 2 mg/m^2 ATX-101 was 0.5% (5/1050). No severe skin ulceration events were reported for either ATX-101 or placebo patients across the clinical development program. All of the events were reported as recovered/resolved. The few ulceration events reported occurred randomly with respect to treatment session.

To reduce the potential for superficial skin ulceration, injection of ATX-101 should be delivered midway into the SC fat layer and injection should not be continued while the needle is being

withdrawn. Instructions to this effect will be provided in the product labeling and in physician training materials.

5.3.11.3. Dysphagia

This category describes events consistent with patient reports of discomfort/difficulty with swallowing. The sensation of dysphagia is attributable to a sensation of fullness in the submental/neck area associated with post injection swelling/edema. In addition to spontaneous reporting of such events by patients, investigators also elicited whether dysphagia symptoms were experienced during treatment.

In the pivotal studies, dysphagia was reported in 10 patients (1.9%; 10 events) in the ATX-101 group and 1 patient (0.2%; 1 event) in the placebo group. Most events were mild, with 2 patients (0.4%) in the ATX-101 group reporting severe events. Subject 23-514-002 reported severe dysphagia with onset 5 days after the first treatment session. The patient received fewer than 6 treatments and discontinued from the study; the event resolved. Subject 23-528-016 reported severe dysphagia with onset 1 day after the fourth treatment session; the event resolved in 2 days. The patient continued to receive additional treatment and completed the study. Among ATX-101 patients who reported dysphagia, the median duration was 3 days and the events resolved in all but one patient. Subject 22-109-023, a 61-year-old female, reported mild dysphagia starting 7 days after the second treatment session that was recorded as unresolved. The patient withdrew from the study 35 days after her second treatment session. Other ongoing events reported at the patient's last visit included mild dysphonia and mild oropharyngeal pain (these events were considered not related to study drug). This patient withdrew consent and declined to return for protocol-specified follow-up visits.

An assessment of dysphagia in the broader safety population of all SMF studies was also conducted (including the patients discussed above in the pivotal studies). Overall, a total of 12 dysphagia events occurred in 12 patients (1.1%) treated with 2 mg/cm^2 ATX-101 across the clinical program. In the placebo group, a total of 2 events occurred in 2 patients (0.2%). Of these, 2 dysphagia events led to patients' receiving fewer than the maximum number of treatments, and 1 event led to discontinuation from study (Subject 23-514-002 discussed above). All but 2 of the dysphagia events resolved in 1 to 7 days (Subject 22-109-023 and Subject 23-514-002, as described above).

Overall, events of dysphagia were reported in a small proportion (1% to 2%) of patients treated with ATX-101, were usually mild in severity, and typically resolved within a few days.

5.4. Other Observations Related to Safety

5.4.1. Long-term Safety

Long-term safety data are available from ongoing Study 12, (ie, patients previously treated in Phase 2 Studies 03 [n = 56], 07 [n = 58] or 15 [n = 91]), Study 1403740 (ie, patients previously treated in EU Phase 3 Studies 16 [n = 101] or 17 [n = 100]), Study 35 (ie, patients previously treated in pivotal Studies 22 [n = 120] and 23 [n = 104]), and open-label treatment and LTFU Study 26 (n = 137 patients who completed Visit 10). Among the 767 patients evaluable for long-term safety, 242 had received placebo and 374 had received ATX-101 at the 2 mg/cm^2 dose used in the pivotal studies. In the ATX-101 2 mg/cm^2 dose group, 71 patients (19.0%) reported 97

AEs during the LTFU period (ie, ≥ 6 months after last treatment) and in the placebo group, 21 patients (8.7%) reported 31 AEs. Many of these AEs (48 in the ATX-101 2 mg/cm^2 group and 23 in the placebo group) had started in the predecessor study and were therefore covered earlier in Section 5.3.

Adverse events that started during the LTFU period were reported in 36 patients (9.6%) in the ATX-101 2 mg/cm^2 group and 7 patients (2.9%) in the placebo group. The only individual AEs that started during the LTFU period and were reported in more than 1 patient treated with ATX-101 (2 mg/cm^2) were hypertension (3 patients [0.8%]), hypothyroidism (2 patients [0.5%]), nasopharyngitis (2 patients [0.5%]), and sinusitis (2 patients [0.5%]). No AE that started during the LTFU period was reported in more than 1 patient in the placebo group. No new safety concerns or signals were identified during the LTFU period.

5.4.2. Clinical Laboratory Results and QT/QTc Intervals

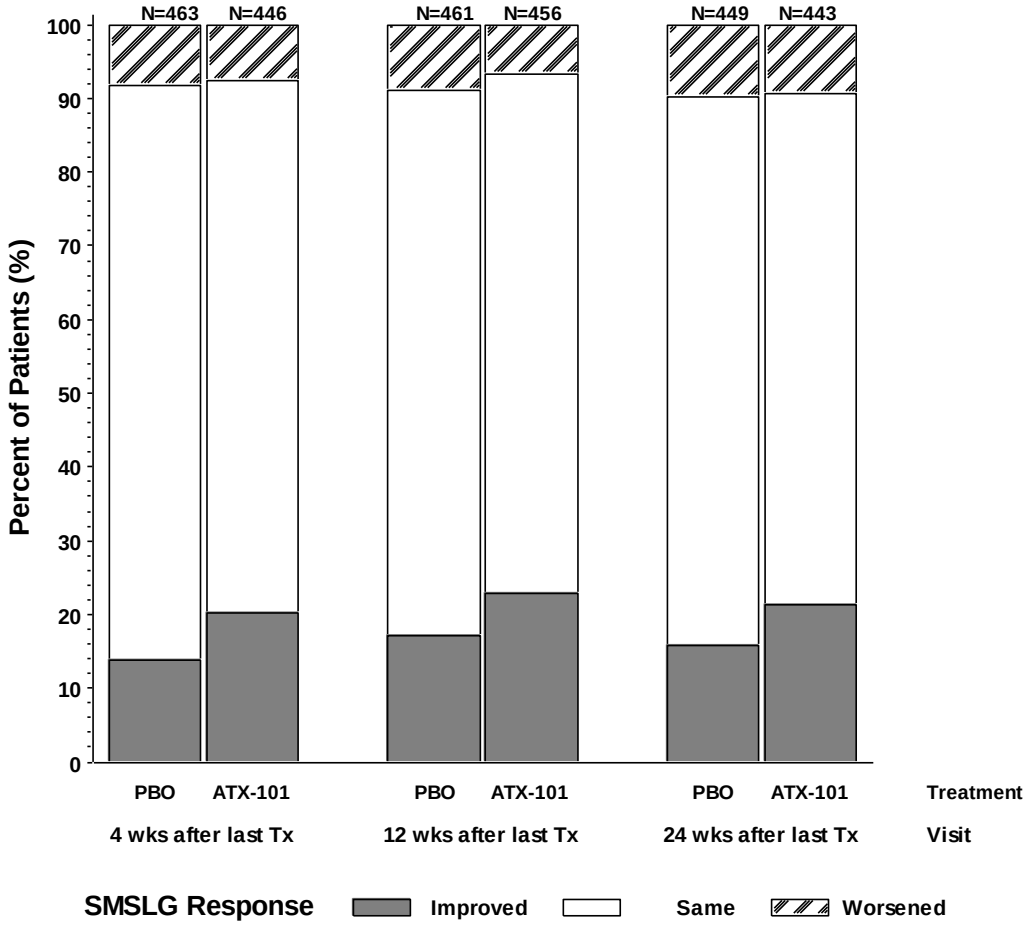
Treatment with ATX-101 was not associated with any clinically meaningful changes in vital signs, liver function tests, renal function tests, serum lipid concentrations, or hematology results. ATX-101 had no effect on QT/QTc intervals.

5.4.3. Skin Laxity

In order to determine whether treatment with ATX-101 might result in worsening of skin laxity in the submental region, skin laxity evaluations were performed in the pivotal studies using a 4-point submental skin laxity grading (SMSLG) scale with demonstrated inter-rater and intra-rater reliability (all intra-class correlation coefficients > 0.8 in nontreatment Study 25).

Despite the majority of patients having reductions in SMF volume, > 90.0% of patients in the pivotal studies were reported to have improved or unchanged skin laxity scores at 12 weeks after last treatment, compared with baseline, based on the SMSLG (Figure 21). It can therefore be concluded that reductions in SMF due to ATX-101 did not result in adverse impacts on skin laxity.

Figure 21: Skin Laxity (SMSLG) Results by Study Visit—Pivotal Studies (Observed)



SMSLG = Submental Skin Laxity Grade.
Note: The SMSLG is scored from 1 to 4, where 1 is none and 4 is severe with respect to skin laxity. "Improved" means a lower rating compared to baseline and "Worsened" means a higher rating compared to baseline.
Source: Integrated Summary of Safety Posttext Table 9.1.2 in NDA 206333

5.5. Safety Conclusions

The safety evaluation program for ATX-101 was comprehensive. It included both spontaneously reported and elicited AEs, acute and late-onset events, ECGs, and clinical laboratory evaluations. Particular attention was also given to a large set of special interest AEs that might be expected to occur given the mode of administration (injection), mechanism of drug action, or the resulting tissue response. In terms of demographic and baseline characteristics, the patient population enrolled in the SMF studies was consistent with the intended population for the marketed drug.

The results from all of these sources present a consistent and favorable safety profile for ATX-101. The results from the pooled pivotal studies are similar to those of the individual studies (Study 22 and Study 23), which were in close agreement with each other. This similarity provides a substantial basis on which conclusions are made in the integrated analysis of the pivotal studies.

The safety results across all SMF clinical studies provide strong confirmation of the primary pivotal study analyses. The results of the LTFU analyses provide confirmation of the durability of the treatment effect and long-term safety of ATX-101.

The safety profile of ATX-101 used in adults for improvement in the appearance of moderate to severe convexity or fullness associated with SMF is well characterized. ATX-101 is an acute, elective, and safe treatment, with mostly transient and mild or moderate AEs related to the treatment area that typically resolve without intervention or sequelae, and that can be managed by the practitioner.

6. SUMMARY AND CONCLUSIONS ON SAFETY AND BENEFIT/RISK

Treatment with ATX-101 represents a nonsurgical, in-office procedure for reduction of SMF with no general anesthesia, and is a less invasive alternative to liposuction with or without neck lift. Current treatment options for reduction of SMF include traditional aesthetic surgical procedures performed under general anesthesia, as well as targeted liposuction, which may be performed under general or local anesthesia.

Across all studies, the efficacy results consistently demonstrate the superiority of ATX-101 relative to placebo in the reduction of SMF. Specifically, the results from 2 identical, randomized, double-blind, placebo-controlled Phase 3 studies conducted in the US and Canada (Studies 22 and 23) represent the pivotal data that support the efficacy of ATX-101. Consistent and clinically meaningful improvements in SMF have been demonstrated in the majority of patients, as reflected by clinician- and patient-reported improvements in the appearance of submental convexity/fullness and by objective measurements based on MRI. The pooled results for Studies 22 and 23 indicated that a 1-grade composite SMFRS response was obtained in 68.2% of ATX-101-treated patients overall compared with 20.5% of placebo-treated patients ($p < 0.001$). A 2-grade composite SMFRS response was obtained in 16.0% of the pooled ATX-101-treated patients compared with 1.5% of the pooled placebo-treated patients ($p < 0.001$). Furthermore, the pooled data indicated that, overall, 43.3% of ATX-101-treated patients and 5.3% placebo-treated patients were considered MRI responders in the pivotal studies. The reported reductions in SMF are also associated with improvement in the impact of SMF on patient's self-perceptions and satisfaction. Results demonstrated that a high proportion of patients were satisfied with the appearance of their face/chin following treatment with ATX-101. At the end of study (Visit 10), 79.1% of patients in the pooled ATX-101 group were SSRS responders, compared to 32.8% of patients in the pooled placebo group ($p < 0.001$). Reductions in SMF following treatment with ATX-101 were seen in patients across studies, and regardless of baseline age, sex, race, ethnicity, amount of SMF (moderate or severe), BMI, and skin laxity. The effects of ATX-101 on the reduction of SMF are durable and have been maintained for up to 4 years following treatment.

Across the clinical development program, treatment with ATX-101 was safe and well tolerated. Results from pivotal Phase 3 Studies 22 and 23 are indicative of the overall safety profile of ATX-101. Safety data from these studies are consistent with results observed in previous ATX-101 studies. The most frequently reported AEs were local reactions at the injection site including hematoma, pain, anesthesia, edema, swelling, erythema, induration, paresthesia, nodule, and pruritus. These local reactions are expected based on the mode of administration (local injection), the pharmacologic action of ATX-101, and the resulting tissue response. Although the majority of patients in ATX-101 clinical studies experienced AEs considered related to ATX-101, most side effects of ATX-101 treatment were temporary and most events had a maximum severity grade of mild or moderate (80.9% and 17.5% of events, respectively) over the course of treatment. Serious AEs were uncommon, being reported by 2.5% of ATX-101 patients and 4.4% of placebo patients in the pivotal studies. Other AESI, such as nerve injury and ulceration, were infrequent, typically mild or moderate in severity, transient, and resolved without treatment.

Adverse events outside of the treatment area were infrequently observed; when observed, they occurred in both the ATX-101 and placebo groups.

Just over half of patients in the pivotal studies completed the maximum of 6 treatment sessions. For patients who did not, approximately 41% in the ATX-101 group, 2 of the most common reasons were insufficient remaining SMF and patient satisfaction with SMF reduction. Relatively few patients treated with ATX-101 (6.8%) received fewer than 6 treatment sessions due to an AE, and only a small percentage of patients treated with ATX-101 (3.1%) did not complete the pivotal Phase 3 studies due to AEs.

No long-term safety issues associated with ATX-101 treatment have been identified to date. Furthermore, the types of AEs observed during LTFU were similar to those observed in the pivotal studies, with fewer injection-site-related events. No new safety concerns or signals were identified.

In conclusion, the efficacy of ATX-101 for improving the appearance of moderate to severe convexity or fullness associated with SMF has been conclusively demonstrated. The safety and tolerability of ATX-101 have been well characterized across a comprehensive development program and are acceptable. Based on this information, adequate directions for use and clear presentations of anticipated benefits and risks will be provided in product labeling. Therefore, given the overall balance of risks and benefits described, ATX-101 represents a safe, effective, and less invasive alternative to current treatment options for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults.

7. RISK MANAGEMENT PLAN

The Sponsor intends to mitigate risk by providing detailed product labeling that will inform health care providers on injection site risks and emphasize techniques to avoid or reduce injection site AEs (eg, neuropraxia, ulceration). In addition, the Sponsor intends to offer comprehensive prescriber injection training to inform physicians on the correct use of ATX-101 in appropriate patients with undesired SMF. Routine pharmacovigilance and monitoring of AEs from the global safety database, as well as postmarketing surveillance to monitor for any rare, but clinically relevant AEs is planned. Details of risk management are presented below.

To ensure adequate oversight of any potential safety concerns associated with ATX-101, Kythera has included sufficient information regarding directions for use and associated risks in the product labeling to allow for the safe use of ATX-101 in the postmarketing setting. Topics covered include the selection of appropriate patients, use of the correct number and locations for injections, proper administration techniques, and pain management options. Prescribers are instructed to screen for other causes of submental fullness such as thyromegaly and cervical lymphadenopathy, and are also advised to carefully consider patients with excessive skin laxity, prominent platysmal bands, scar tissue, prior surgical or aesthetic procedures in the treatment area, or other conditions for which reduction of SMF may result in an aesthetically undesirable outcome. Caution is advised in cases where patients have a history of dysphagia or facial neuropraxia, or have inflammation or induration at the treatment area.

Injection technique is outlined in the package insert, such as injecting perpendicular to the skin surface, mid-way into the SC fat and not injecting during withdrawal of the syringe to avoid superficial injections into the dermis that may lead to ulceration or inadvertent injection into salivary glands, lymph nodes, or muscles. Detailed directions are provided to decrease the risk for motor neuropraxia (of the marginal mandibular nerve), including avoiding injection above the inferior border of the mandible and within a 3-cm radius circle centered at a point approximately 2 cm lateral to and 2 cm inferior to the oral commissure.

In addition to what is provided in the package insert, an injection training program will be offered to physicians in multiple formats, including web-based and/or live sessions at educational meetings or the physician's office. This training will include a detailed review of cervicomental anatomy and thorough demonstrations of patient assessment, ATX-101 injection technique, and patient comfort management. The effectiveness of the injection technique training will be assessed periodically and modified as appropriate. For example, an injection training video will be used to demonstrate the correct clinical procedures, including proper injection technique, for the administration of ATX-101.

In order to develop an understanding of the condition of submental fullness due to SMF, how it is treated in current clinical practice, and the risks and benefits associated with its treatment, Kythera is planning to conduct a prospective, observational, multicenter registry study (Study ATX-101-15-40M; Condition of Submental Fullness and Treatment Outcomes Registry [CONTOUR]). This registry will involve the systematic collection of data on the population of physicians with patients who have SMF concerns, the population of patients who are eligible for SMF reduction treatment, eligible patients who elect SMF reduction treatment, treatment procedures, and treatment outcomes.

Based on the safety profile of ATX-101 characterized by transient, mild or moderate AEs occurring predominantly in the treatment area, it is reasonable that patients, in consultation with their physicians, will be able to weigh the benefits and risks of treatment with ATX-101 and decide whether or not to initiate and/or continue additional treatment without putting the patient at undue risk.

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9. APPENDICES

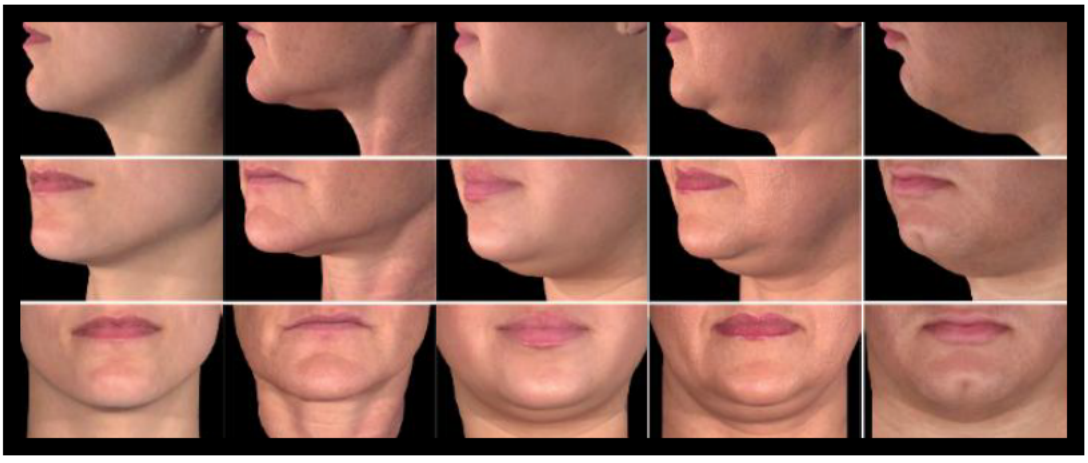
APPENDIX A. CLINICIAN-REPORTED SUBMENTAL FAT RATING SCALE (CR-SMFRS)

Score	SMF Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

Note: The score is based on a static live assessment by the physician

Representative Photographs

CR-SMFRS Score				
0	1	2	3	4



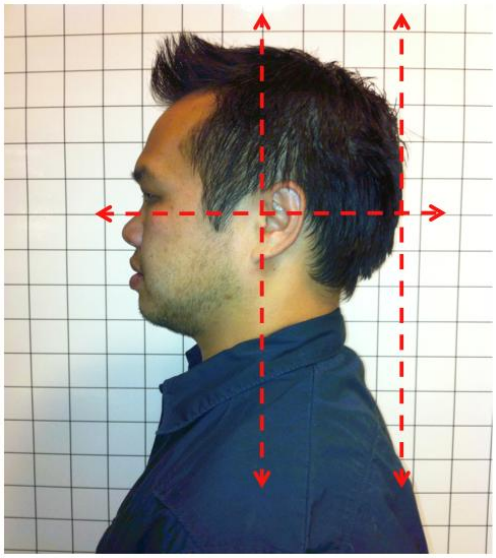
CR-SMFRS Assessment Procedures

CR-SMFRS score is based on investigator's clinical evaluation of the patient, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head.

Each center will be provided with the CR-SMFRS book containing the representative photographs for each score and a 2-inch by 2-inch grid poster that will be placed on the wall, with the horizontal lines parallel to the floor, in the area where ratings will be conducted.

The score is determined using the definitions in the rating scale and representative photographs associated with each score. In order to maintain a consistent posture from which the scores will be made, the final determination of the score will be made while the patient's head is in the Frankfort plane posture. The correct posture will be achieved as in the example below using the following:

1. Position the patient standing facing to the rater's left approximately 1 foot in front of the grid.
2. The rater will stand such that he or she can visualize the horizontal lines on the grid to be parallel to the plane from the patient's lower orbital arch of the eye to the cephalic margin of the tragus of the ear. This is the Frankfort plane.
3. While the patient is in the correct position relative to the horizontal plane, the rater will visualize the vertical lines to line-up with the tragus and the front of the patient's shoulder. Alternatively a vertical line can be used that aligns with the back of the patient's head on a plane slightly posterior to the patient's shoulder.



The score will be recorded as a whole number. At screening, the score is determined in conjunction with protocol entry criteria (eg, absence of loose skin, diffuse submental fat, and prominent platysmal bands at rest that interfere with evaluation of localized fat).

APPENDIX B. PATIENT-REPORTED SUBMENTAL FAT RATING SCALE (PR-SMFRS)

The patient is instructed to position his or her head in a manner similar to that described for CR-SMFRS assessment and asked to respond via static live assessment to the question below.

PR-SMFRS

Please look in the mirror at **the area under your chin** to help you answer the following question:

How much fat do you have under your chin right now? Mark ☒ in one box below	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

APPENDIX C. PATIENT-REPORTED SUBMENTAL FAT IMPACT SCALE (PR-SMFIS)

PR-SMFIS

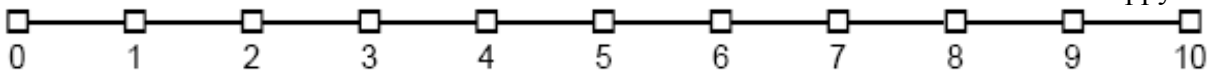
Please look in the mirror at the area under your chin to help you answer the following questions:

1.

How happy are you with the appearance of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not happy at all — Extremely happy

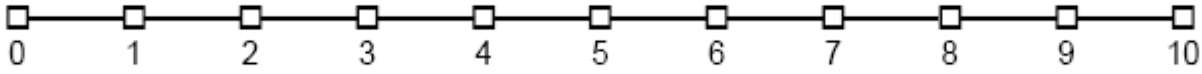


2.

How bothered are you by the appearance of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not bothered at all — Extremely bothered

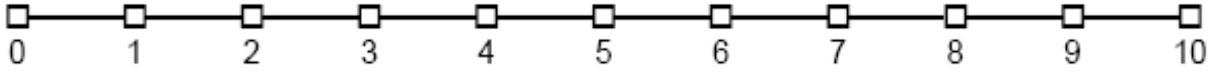


3.

How self-conscious are you about the appearance of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not self-conscious at all — Extremely self-conscious



PR-SMFIS (continued)

4.

How embarrassed are you about the appearance of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not embarrassed at all — Extremely embarrassed

0 1 2 3 4 5 6 7 8 9 10

5.

How much older do you look because of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not older at all — Very much older

0 1 2 3 4 5 6 7 8 9 10

6.

How much overweight do you look because of your chin fat?

Mark ☒ in one box below and do not mark between the boxes

Not overweight at all — Extremely overweight

0 1 2 3 4 5 6 7 8 9 10

APPENDIX D. SUBJECT SELF-RATING SCALE (SSRS)

The patient will be asked to respond to the question below. No photographs or reference to previous ratings or evaluations will be used.

Baseline: Considering your appearance in association with your face and chin, how satisfied do you feel with your appearance at the present time?

0 - Extremely dissatisfied

1 - Dissatisfied

2 - Slightly dissatisfied

3 - Neither satisfied nor dissatisfied

4 - Slightly satisfied

5 - Satisfied

6 - Extremely satisfied

Postbaseline: Considering your appearance in association with your face and chin, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with ATX-101?

0 - Extremely dissatisfied

1 - Dissatisfied

2 - Slightly dissatisfied

3 - Neither satisfied nor dissatisfied

4 - Slightly satisfied

5 - Satisfied

6 - Extremely satisfied

APPENDIX E. SUBJECT GLOBAL QUESTIONS

1.

Since the start of this study, how would you rate the fat under your chin right now? Mark ☒ in one box below	
☐	A great deal worse
☐	Moderately worse
☐	A little worse
☐	About the same
☐	A little better
☐	Moderately better
☐	A great deal better

2.

Since the start of this study, how would you rate the definition between your chin and neck right now? Mark ☒ in one box below	
☐	A great deal worse
☐	Moderately worse
☐	A little worse
☐	About the same
☐	A little better
☐	Moderately better
☐	A great deal better

3.

How satisfied are you with the treatment you received in this study? Mark ☒ in one box below	
☐	Extremely dissatisfied
☐	Moderately dissatisfied
☐	A little dissatisfied
☐	Neither dissatisfied or satisfied
☐	A little satisfied
☐	Moderately satisfied
☐	Extremely satisfied

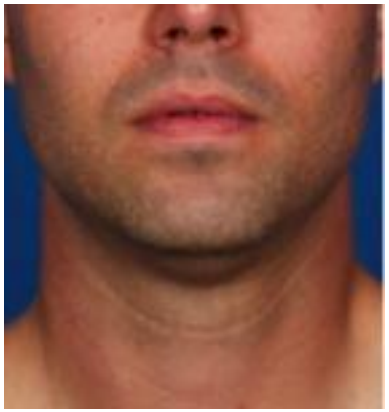
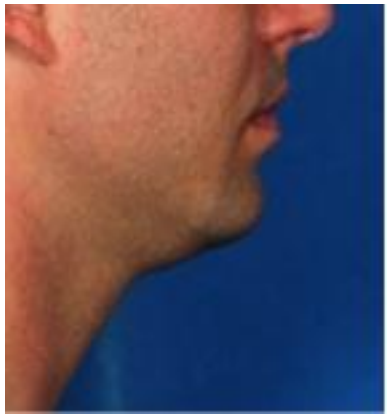
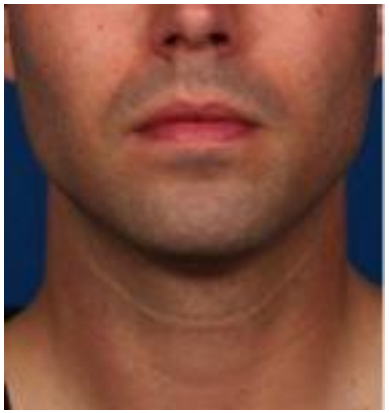
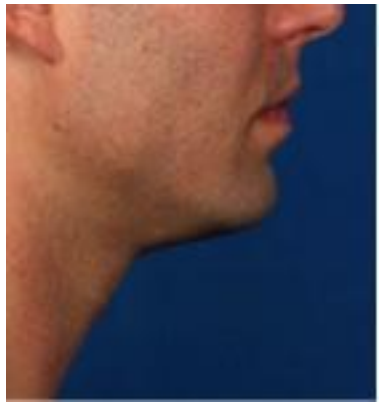
Scoring

Q#1 and Q#2: 1 = a great deal worse, 4 = about the same, 7 = a great deal better.

Q#3: 1 = extremely dissatisfied, 4 = neither dissatisfied nor satisfied, 7 = extremely satisfied.

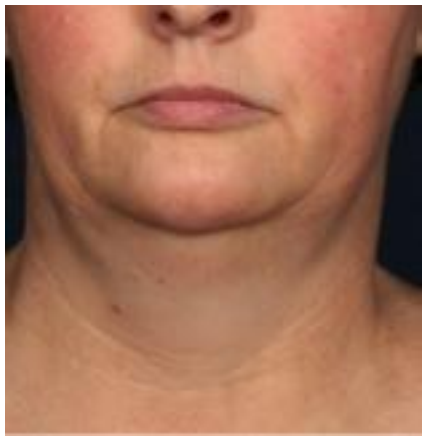
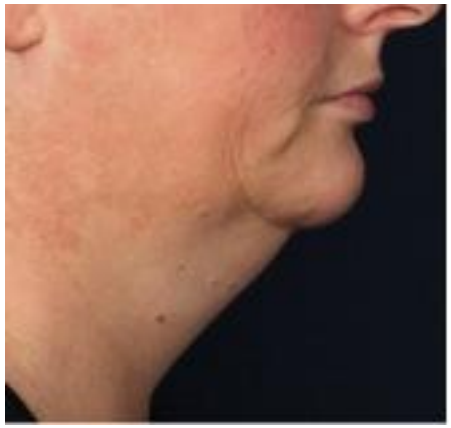
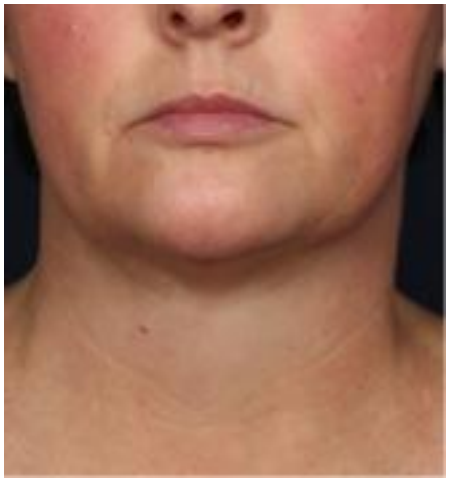
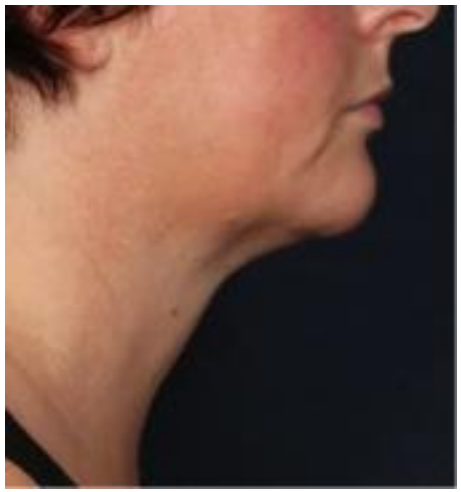
APPENDIX F. SAMPLE PHOTOGRAPHS FROM STUDIES 22 AND 23

Patient Photos – 1 Grade Composite Change (Study 22)

<table>
<tr>
<td>Age 34
Baseline
BMI: 24.4
Weight: 170 lbs.</td>
<td>  </td>
<td>  </td>
<td>Study 22
CR-SMFRS: 2
PR-SMFRS: 2
Satisfaction*
Dissatisfied
Skin Laxity*
None</td>
</tr>
<tr>
<td>12 Weeks after Last Treatment
BMI: 25.8
Weight: 179.5 lbs.</td>
<td>  </td>
<td>  </td>
<td>CR-SMFRS: 1
PR-SMFRS: 1
Satisfaction*
Satisfied
Skin Laxity*
None</td>
</tr>
<tr>
<td colspan="4">Number of Treatment Cycles: 5</td>
</tr>
</table>

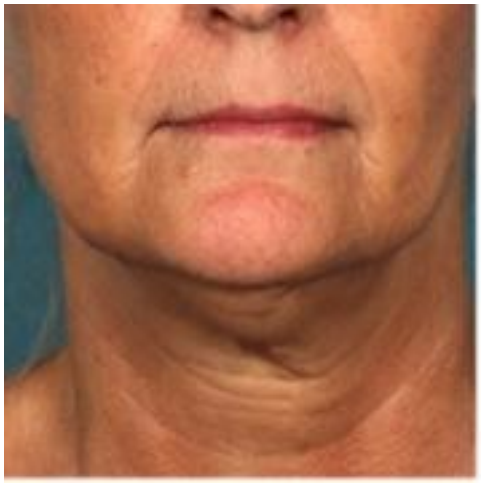
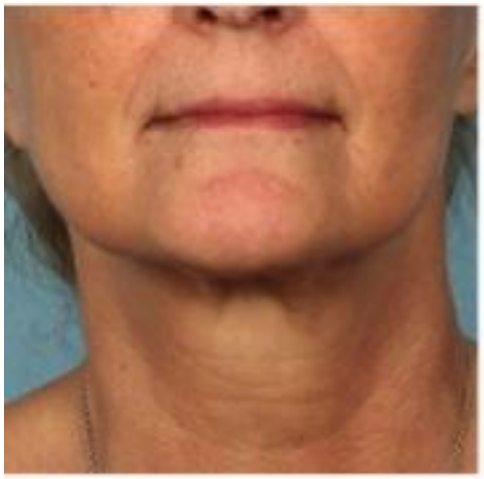
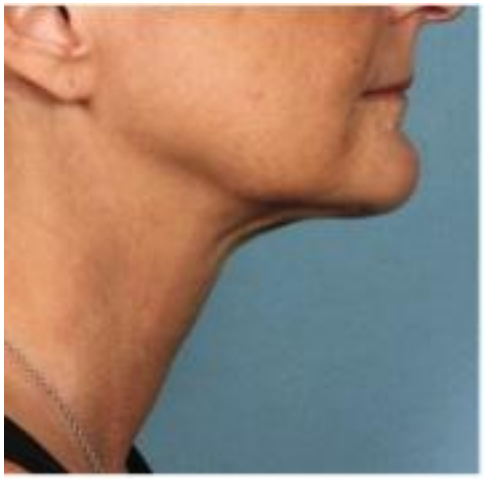
*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)

Patient Photos – 1 Grade Composite Change (Study 22)

Age 45 Baseline *BMI*: 26.1 *Weight*: 156 lbs.			Study 22 CR-SMFRS: 3 PR-SMFRS: 2 *Satisfaction** Extremely dissatisfied *Skin Laxity** Mild
12 Weeks after Last Treatment *BMI*: 27.9 *Weight*: 167 lbs.			CR-SMFRS: 1 PR-SMFRS: 1 *Satisfaction** Extremely satisfied *Skin Laxity** Mild
Number of Treatment Cycles: 4			

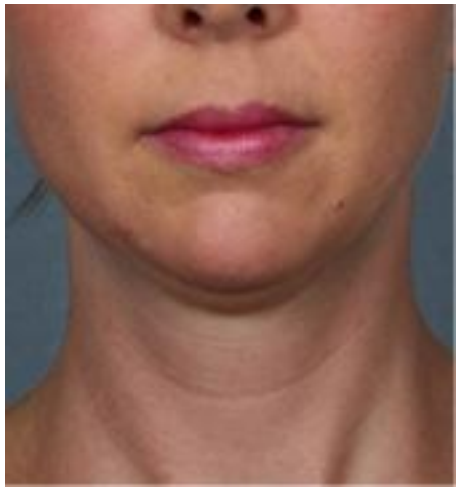
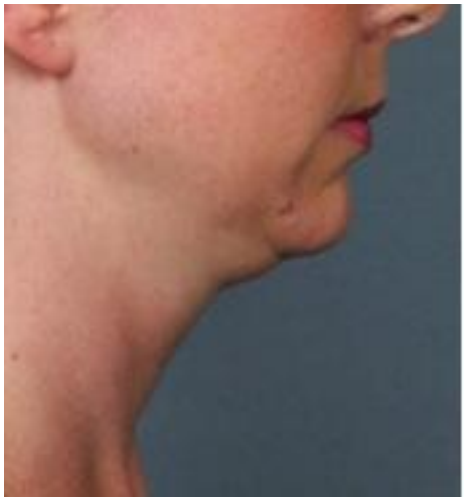
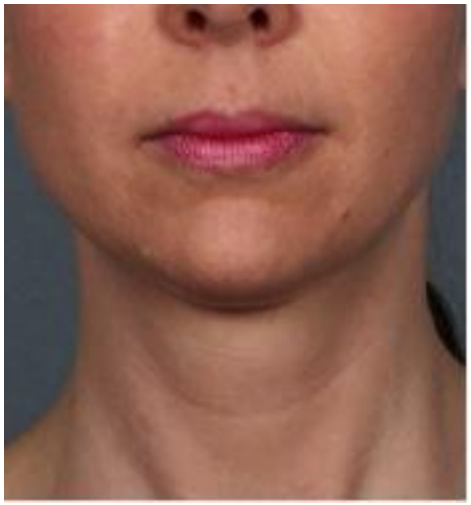
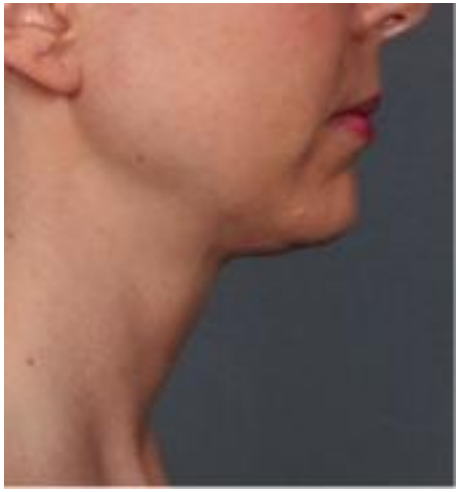
*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)

Patient Photos – 1 Grade Composite Change (Study 22)

Age 55 Baseline *BMI*: 21.8 *Weight*: 150 lbs.			Study 22 CR-SMFRS: 2 PR-SMFRS: 2 *Satisfaction** Dissatisfied *Skin Laxity** Mild
12 Weeks after Last Treatment *BMI*: 21.8 *Weight*: 150 lbs.			CR-SMFRS: 1 PR-SMFRS: 1 *Satisfaction** Somewhat satisfied *Skin Laxity** Moderate
Number of Treatment Cycles: 5			

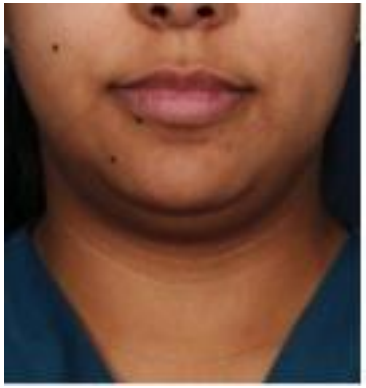
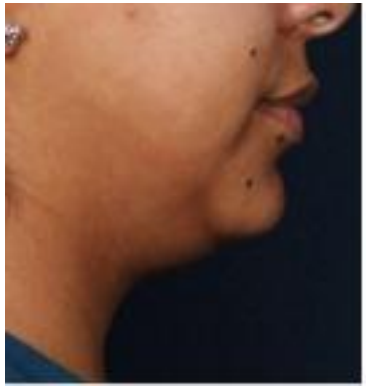
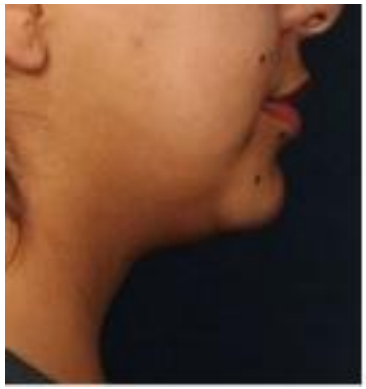
*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)

Patient Photos – 1 Grade Composite Change (Study 23)

<table>
<tr>
<td>Age 35
Baseline
BMI: 20
Weight: 115.3 lbs.</td>
<td>  </td>
<td>  </td>
<td>Study 23
CR-SMFRS: 2
PR-SMFRS: 2
Satisfaction*
Dissatisfied
Skin Laxity*
None</td>
</tr>
<tr>
<td>12 Weeks after Last Treatment
BMI: 19.6
Weight: 113.1 lbs.</td>
<td>  </td>
<td>  </td>
<td>CR-SMFRS: 0
PR-SMFRS: 1
Satisfaction*
Satisfied
Skin Laxity*
None</td>
</tr>
<tr>
<td colspan="4">Number of Treatment Cycles: 4</td>
</tr>
</table>

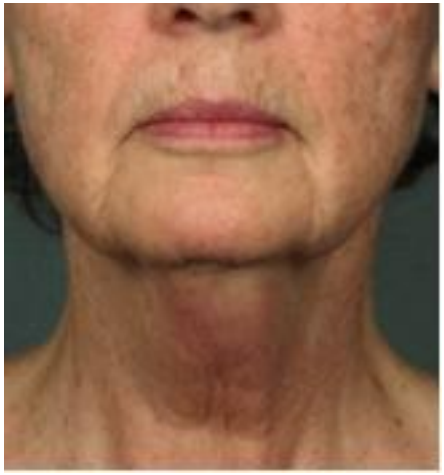
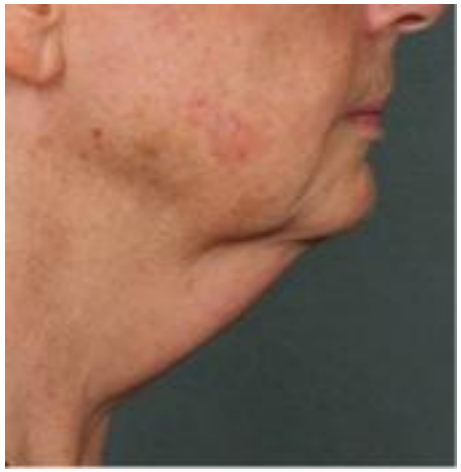
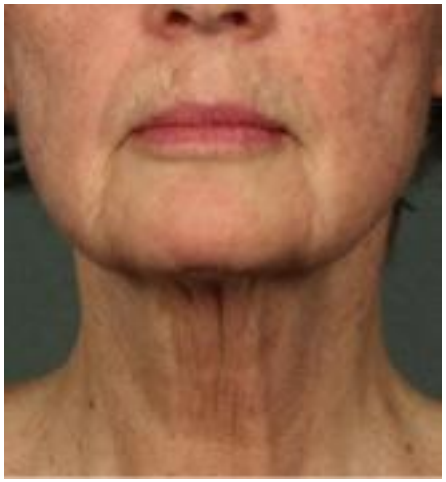
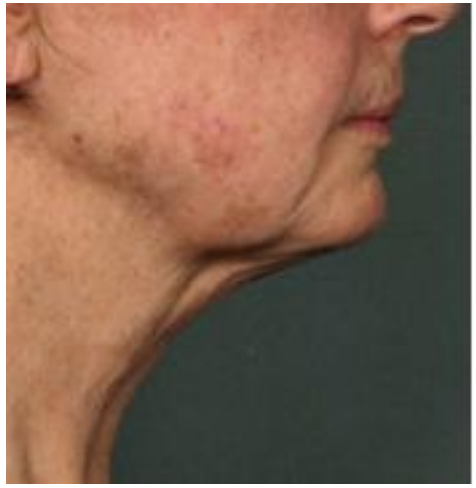
*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)

Patient Photos – 2 Grade Composite Change (Study 22)

Age 26 Baseline *BMI*: 26.2 *Weight*: 133 lbs.			Study 22 CR-SMFRS: 2 PR-SMFRS: 3 *Satisfaction** Extremely dissatisfied *Skin Laxity** None
12 Weeks after Last Treatment *BMI*: 26.4 *Weight*: 134 lbs.			CR-SMFRS: 0 PR-SMFRS: 1 *Satisfaction** Extremely satisfied *Skin Laxity** None
Number of Treatment Cycles: 6			

*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)

Patient Photos – 2 Grade Composite Change (Study 23)

Age 55 Baseline *BMI*: 24.3 *Weight*: 156.2 lbs.			Study 23 CR-SMFRS: 3 PR-SMFRS: 3 *Satisfaction** Dissatisfied *Skin Laxity** Moderate
12 Weeks after Last Treatment *BMI*: 23.9 *Weight*: 154 lbs.			CR-SMFRS: 1 PR-SMFRS: 1 *Satisfaction** Satisfied *Skin Laxity** Moderate
Number of Treatment Cycles: 6			

*Satisfaction based on Subject Self-rating Scale (SSRS); laxity based on Submental Skin Laxity Grading Scale (SMSLG)